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(54) Title: 71 HUMAN SECRETED PROTEINS

(57) Abstract: The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/29871

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07H 21/04; C07K 14/435
US CL : 536/23.5; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.5; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ✓	Database NCBI, accession number AC012267, Homo Sapiens Clone, 26 May 2000, see entire document.	1, 5-7
X ✓	WO 00/04140 A1 (HUMAN GENOME SCIENCES, INC.) 27 January 2000, especially pages 223-228, 301-303, and SEQ ID NO's 11, 103, and 195, see entire document.	1-12, 14, 21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
22 March 2003 (22.03.2003)

Date of mailing of the international search report
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-12, 14, 21 and SEQ ID NO's 11 and 104

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-12,14, and 21 drawn to a nucleic acid molecule, a polypeptide encoded by the nucleic acid molecule, a gene, vector and a recombinant cell comprising the nucleic acid molecule, and a method of making the recombinant cell.

Group II, claim(s) 13, drawn to an isolated antibody.

Group III, claim(s) 15-16, drawn to a polypeptide and a method of making the polypeptide.

Group IV, claim(s) 17, drawn to a method of treating, preventing, or ameliorating a condition using a polypeptide or polynucleotide.

Group V, claim(s) 18, drawn to a method of diagnosis using a polynucleotide.

Group VI, claim(s) 19, drawn to a method of diagnosis using a polypeptide.

Group VII, claim(s) 20 and 23, drawn to a method for identifying a binding partner for a polypeptide.

Group VIII, claim(s) 22, drawn to a method for identifying activity in a biological assay.

Each of Groups I-VIII above is further restricted to a single polynucleotide and/or polypeptide sequence. Each polynucleotide sequence is considered an individual structure, therefore each sequence represents a separate product. As a polypeptide is encoded by a polynucleotide, then the polypeptide so encoded is inextricably linked to the polynucleotide encoding it. For this reason, election of a polynucleotide sequence is considered to include election of the polypeptide encoded.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: polynucleotides recited in the claims (e.g. those comprising SEQ ID NO: 11) are known in the prior art, as are polypeptides comprising SEQ ID NO: 104 (the peptide encoded by SEQ ID NO: 11). See the Search Report. As the sequences are known in the art, the claims do not recite a special technical feature and are not linked by a general inventive concept, and therefore lack unity.

INTERNATIONAL SEARCH REPORT

PCT/US01/29871

Continuation of B. FIELDS SEARCHED Item 3:
EST, GENEMBL, GENESEQ, BLOSUM62, PIR_73, SWISSPROT, USpatents, US published applications
for: SEQ ID NO's 11 and 104, and oligomers

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[Continued on next page]

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71 Human Secreted Proteins

Field of the Invention

The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eukaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Thus there exists a clear need for identifying and using novel secreted polynucleotides and polypeptides. Identification and sequencing of human genes is a major goal of modern scientific research. For example, by identifying genes and determining their sequences, scientists have been able to make large quantities of valuable human "gene products." These include human insulin, interferon, Factor VIII, tumor necrosis factor, human growth hormone, tissue plasminogen activator, and numerous other compounds. Additionally, knowledge of gene sequences can provide the key to treatment or cure of genetic diseases (such as muscular dystrophy and cystic fibrosis).

Summary of the Invention

The present invention relates to novel secreted proteins. More specifically, isolated nucleic acid molecules are provided encoding novel secreted polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further

relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Polynucleotides and Polypeptides

Description of Table 1A

Table 1A summarizes information concerning certain polypnucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCC Deposit Number and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEQ ID NO:X. In the ninth column, the nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly , in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the

eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A and/or elsewhere herein

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater

than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Also provided in Table 1A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All

Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC Deposit No.Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA

contained in ATCC Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC Deposit No.Z.

Description of Table 1B

Table 1B summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1A and/or 1B. The third column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1B. The fourth column provides the sequence identifier, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1A and/or 1B. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1B as SEQ ID NO:Y (column 6). Column 7 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1B as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1B. It will be

appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 8, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ^{33}P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 9 provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding

exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

Description of Table 1C

Table 1C summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

Description of Table 1D

Table 1D: In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "FEATURES OF PROTEIN" sections (below) and also as listed in the "Preferred Indications" column of Table 1D (below); comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) represented by Table 1A and Table 1D (in the same row as the disease or disorder to be treated is listed in the "Preferred Indications" column of Table 1D) in an amount effective to treat, prevent, or ameliorate the disease or disorder.

As indicated in Table 1D, the polynucleotides, polypeptides, agonists, or antagonists of the present invention (including antibodies) can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists thereof (including antibodies) could be used to treat the associated disease.

The present invention encompasses methods of preventing, treating, diagnosing, or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indications" column of Table 1D; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to treat, prevent, diagnose, or ameliorate the disease or disorder. The first and seccond columns of Table 1D show the "Gene No." and "cDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in preventing, treating, diagnosing, or ameliorating the disease(s) or disorder(s) indicated in the corresponding row in Column 3 of Table 1D.

In another embodiment, the present invention also encompasses methods of preventing, treating, diagnosing, or ameliorating a disease or disorder listed in the "Preferred Indications" column of Table 1D; comprising administering to a patient

combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in Column 3 of Table 1D.

The "Preferred Indication" column describes diseases, disorders, and/or conditions that may be treated, prevented, diagnosed, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

The recitation of "Cancer" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof) may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., leukemias, cancers, and/or as described below under "Hyperproliferative Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D may be used for example, to diagnose, treat, prevent, and/or ameliorate a neoplasm located in a tissue selected from the group consisting of: colon, abdomen, bone, breast, digestive system, liver, pancreas, prostate, peritoneum, lung, blood (e.g., leukemia), endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), uterus, eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a pre-neoplastic condition, selected from the group consisting of: hyperplasia (e.g., endometrial hyperplasia and/or as described in the section entitled "Hyperproliferative Disorders"), metaplasia (e.g., connective tissue metaplasia, atypical metaplasia, and/or as described in the section entitled "Hyperproliferative Disorders"), and/or dysplasia (e.g., cervical dysplasia, and bronchopulmonary dysplasia).

In another specific embodiment, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cancer" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose,

treat, prevent, and/or ameliorate a benign dysproliferative disorder selected from the group consisting of: benign tumors, fibrocystic conditions, tissue hypertrophy, and/or as described in the section entitled "Hyperproliferative Disorders".

The recitation of "Immune/Hematopoietic" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having the "Immune/Hematopoietic" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, asthma, AIDS, autoimmune disease, rheumatoid arthritis, granulomatous disease, immune deficiency, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, systemic lupus erythematosis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and allergies.

The recitation of "Reproductive" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the reproductive system (e.g., as described below under "Reproductive System Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Reproductive" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cryptorchism, prostatitis, inguinal hernia, varicocele, leydig cell tumors, verrucous carcinoma, prostatitis, malacoplakia, Peyronie's disease, penile carcinoma, squamous cell hyperplasia, dysmenorrhea, ovarian adenocarcinoma, Turner's syndrome, mucopurulent cervicitis, Sertoli-leydig tumors, ovarian cancer, uterine cancer, pelvic inflammatory disease, testicular cancer, prostate cancer, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, testicular atrophy, testicular feminization, anorchia, ectopic testis, epididymitis, orchitis, gonorrhea, syphilis, testicular torsion, vasitis nodosa, germ cell tumors, stromal tumors, dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding, cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, cervical neoplasms, pseudohermaphroditism, and premenstrual syndrome.

The recitation of "Musculoskeletal" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the immune system (e.g., as described below under "Immune Activity").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Musculoskeletal" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: bone cancers (e.g., osteochondromas, benign chondromas, chondroblastoma, chondromyxoid fibromas, osteoid osteomas, giant cell tumors,

multiple myeloma, osteosarcomas), Paget's Disease, rheumatoid arthritis, systemic lupus erythematosus, osteomyelitis, Lyme Disease, gout, bursitis, tendonitis, osteoporosis, osteoarthritis, muscular dystrophy, mitochondrial myopathy, cachexia, and multiple sclerosis.

The recitation of "Cardiovascular" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Cardiovascular" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: myxomas, fibromas, rhabdomyomas, cardiovascular abnormalities (e.g., congenital heart defects, cerebral arteriovenous malformations, septal defects), heart disease (e.g., heart failure, congestive heart disease, arrhythmia, tachycardia, fibrillation, pericardial Disease, endocarditis), cardiac arrest, heart valve disease (e.g., stenosis, regurgitation, prolapse), vascular disease (e.g., hypertension, coronary artery disease, angina, aneurysm, arteriosclerosis, peripheral vascular disease), hyponatremia, hypernatremia, hypokalemia, and hyperkalemia.

The recitation of "Mixed Fetal" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Mixed Fetal" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: spina bifida, hydranencephaly, neurofibromatosis, fetal alcohol syndrome, diabetes

mellitus, PKU, Down's syndrome, Patau syndrome, Edwards syndrome, Turner syndrome, Apert syndrome, Carpenter syndrome, Conradi syndrome, Crouzon syndrome, cutis laxa, Cornelia de Lange syndrome, Ellis-van Creveld syndrome, Holt-Oram syndrome, Kartagener syndrome, Meckel-Gruber syndrome, Noonan syndrome, Pallister-Hall syndrome, Rubinstein-Taybi syndrome, Scimitar syndrome, Smith-Lemli-Opitz syndrome, thromocytopenia-absent radius (TAR) syndrome, Treacher Collins syndrome, Williams syndrome, Hirschsprung's disease, Meckel's diverticulum, polycystic kidney disease, Turner's syndrome, and gonadal dysgenesis, Klippel-Feil syndrome, Ostogenesis imperfecta, muscular dystrophy, Tay-Sachs disease, Wilm's tumor, neuroblastoma, and retinoblastoma.

The recitation of "Excretory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and renal disorders (e.g., as described below under "Renal Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Excretory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: bladder cancer, prostate cancer, benign prostatic hyperplasia, bladder disorders (e.g., urinary incontinence, urinary retention, urinary obstruction, urinary tract Infections, interstitial cystitis, prostatitis, neurogenic bladder, hematuria), renal disorders (e.g., hydronephrosis, proteinuria, renal failure, pyelonephritis, urolithiasis, reflux nephropathy, and unilateral obstructive uropathy).

The recitation of "Neural/Sensory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the nervous system (e.g., as described below under "Neural Activity and Neurological Diseases").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Neural/Sensory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: brain cancer (e.g., brain stem glioma, brain tumors, central nervous system (Primary) lymphoma, central nervous system lymphoma, cerebellar astrocytoma, and cerebral astrocytoma, neurodegenerative disorders (e.g., Alzheimer's Disease, Creutzfeldt-Jakob Disease, Parkinson's Disease, and Idiopathic Presenile Dementia), encephalomyelitis, cerebral malaria, meningitis, metabolic brain diseases (e.g., phenylketonuria and pyruvate carboxylase deficiency), cerebellar ataxia, ataxia telangiectasia, and AIDS Dementia Complex, schizophrenia, attention deficit disorder, hyperactive attention deficit disorder, autism, and obsessive compulsive disorders.

The recitation of "Respiratory" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the respiratory system (e.g., as described below under "Respiratory Disorders").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Respiratory" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cancers of the respiratory system such as larynx cancer, pharynx cancer, trachea cancer, epiglottis cancer, lung cancer, squamous cell carcinomas, small cell (oat cell) carcinomas, large cell carcinomas, and adenocarcinomas. Allergic reactions, cystic fibrosis, sarcoidosis, histiocytosis X, infiltrative lung diseases (e.g., pulmonary fibrosis and lymphoid interstitial pneumonia), obstructive airway diseases (e.g., asthma, emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis and asbestosis), pneumonia, and pleurisy.

The recitation of "Endocrine" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the respiratory system (e.g., as described below under "Respiratory Disorders"), renal disorders (e.g., as described below under "Renal Disorders"), and disorders of the endocrine system (e.g., as described below under "Endocrine Disorders".

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having an "Endocrine" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: cancers of endocrine tissues and organs (e.g., cancers of the hypothalamus, pituitary gland, thyroid gland, parathyroid glands, pancreas, adrenal glands, ovaries, and testes), diabetes (e.g., diabetes insipidus, type I and type II diabetes mellitus), obesity, disorders related to pituitary glands (e.g., hyperpituitarism, hypopituitarism, and pituitary dwarfism), hypothyroidism, hyperthyroidism, goiter, reproductive disorders (e.g. male and female infertility), disorders related to adrenal glands (e.g., Addison's Disease, corticosteroid deficiency, and Cushing's Syndrome), kidney cancer (e.g., hypernephroma, transitional cell cancer, and Wilm's tumor), diabetic nephropathy, interstitial nephritis, polycystic kidney disease, glomerulonephritis (e.g., IgM mesangial proliferative glomerulonephritis and glomerulonephritis caused by autoimmune disorders; such as Goodpasture's syndrome), and nephrocalcinosis.

The recitation of "Digestive" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders") and diseases or disorders of the gastrointestinal system (e.g., as described below under "Gastrointestinal Disorders".

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Digestive" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: ulcerative colitis, appendicitis, Crohn's disease, hepatitis, hepatic encephalopathy, portal hypertension, cholelithiasis, cancer of the digestive system (e.g., biliary tract cancer, stomach cancer, colon cancer, gastric cancer, pancreatic cancer, cancer of the bile duct, tumors of the colon (e.g., polyps or cancers), and cirrhosis), pancreatitis, ulcerative disease, pyloric stenosis, gastroenteritis, gastritis, gastric atropy, benign tumors of the duodenum, distension, irritable bowel syndrome, malabsorption, congenital disorders of the small intestine, bacterial and parasitic infection, megacolon, Hirschsprung's disease, aganglionic megacolon, acquired megacolon, colitis, anorectal disorders (e.g., anal fistulas, hemorrhoids), congenital disorders of the liver (e.g., Wilson's disease, hemochromatosis, cystic fibrosis, biliary atresia, and alpha1-antitrypsin deficiency), portal hypertension, cholelithiasis, and jaundice.

The recitation of "Connective/Epithelial" in the "Preferred Indication" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level "), angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity "), and or to promote or inhibit regeneration (e.g., as described below under "Regeneration "), and wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation").

In specific embodiments, a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) having a "Connective/Epithelial" recitation in the "Preferred Indication" column of Table 1D, may be used for example, to diagnose, treat, prevent, and/or ameliorate a disease or disorder selected from the group consisting of: connective tissue metaplasia, mixed connective tissue disease, focal epithelial hyperplasia, epithelial metaplasia, mucoepithelial dysplasia, graft v. host disease, polymyositis, cystic hyperplasia, cerebral dysplasia, tissue hypertrophy,

Alzheimer's disease, lymphoproliferative disorder, Waldenstron's macroglobulinemia, Crohn's disease, pernicious anemia, idiopathic Addison's disease, glomerulonephritis, bullous pemphigoid, Sjogren's syndrome, diabetes mellitus, cystic fibrosis, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, osteoporosis, osteocarthritis, periodontal disease, wound healing, relapsing polychondritis, vasculitis, polyarteritis nodosa, Wegener's granulomatosis, cellulitis, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenese imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, and cutis laxa.

Description of Table 1E

Table 1E provides information related to biological activities and preferred indications for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1E also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID No:Z") provides the unique clone identifier for each clone as previously described and indicated in Tables 1A, 1B, 1C, and 1D. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, 1B, and 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and provides information pertaining to the various

types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity. The sixth column ("Preferred Indications") describes particular embodiments of the invention and indications (e.g. pathologies, diseases, disorders, abnormalities, etc.) for which polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) may be used in detecting, diagnosing, preventing, and/or treating.

Table 1E describes the use of FMAT technology, *inter alia*, for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound flurophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. *See*, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using flourometric microvolume assay technology," Journal of Biomolecular Screening; 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

Table 1E also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a

wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, ERK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

Description of Table 2

Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA clone disclosed in Table 1A or 1B. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1B and allowing for correlation with the information in Table 1B. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

Description of Table 3

Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1B. The second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1A and/or 1B. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1B. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

Description of Table 4

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B, column 8. Column 1 provides the tissue/cell source identifier code disclosed in Table 1B, Column 8. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking

the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

Description of Table 5

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B, column 10. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B, column 9, as determined using the Morbid Map database.

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of

a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 5 of Table 1A), or cDNA clone (as described in column 2 of Table 1A and contained within a pool of plasmids deposited with the ATCC in ATCC Deposit No:Z). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without a natural or artificial signal sequence, the protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, a representative plasmid containing the sequence of SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC") and/or described in Table 1A. As shown in Table 1A, each cDNA is identified by a cDNA clone identifier and the ATCC Deposit Number (ATCC Deposit No:Z). Plasmids that were pooled and deposited as a single deposit have the same ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein) and/or sequences of the cDNA contained in the deposited clone (e.g., the complement of any one, two, three, four, or more of the polynucleotide

fragments described herein). "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 μg/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or

DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a polynucleotide sequence described in column 5 of Table 1A, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 10 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 6 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:2 is the first polypeptide sequence shown in the sequence

listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:3, and so on.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992)).

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where

dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

This gene is expressed primarily in pancreas islet cell tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the pancreas, including cancer and diabetes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pancreas, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: PFCSGFFPSLWIYLPFIFNVSDLWMGSLSGCALPFCLXVFFLTVSPSAVGLLXF AGGPLQTLFAWVSPVEAAEQQRLLPVLSSGSFVSEGTCQMPARALLYEVSVG PYWEIPPSQDTRRSGTYLRRQSDP (SEQ ID NO: 197). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The tissue distribution in tumors of pancreatic islet cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment and intervention of such tumors, in addition to other endocrine or gastrointestinal tumors where expression has been indicated. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: HEGSCRAPGFSAHKGRGCPSPRMTLPSRALASLGVGVWGMLRLNQVTVSCG GSRWSSRVALGAFSWVCGV ALVLQPSGGGLGLTSPSEGCWEGELALAVLRAPGGSPS (SEQ ID NO: 198). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed equally in hemangiopericytoma cells, breast lymph node tissue, and bone marrow.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

immune and hematopoietic disorders, particularly leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hemolymphoid, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 105 as residues: Gly-29 to Ser-35, Ser-63 to Cys-68. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in hemangiopericytoma, breast lymph node, and bone marrow indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The protein product of this gene shares homology with Drosophila, mouse, and human Slit proteins (See Genbank Accession Numbers (protein) AAD25539 and AAD38940; all references available through this accession are hereby incorporated herein by reference; for example Rothberg et al., Genes Dev. 4:2169-87 (1990), Brose K., et al., Cell 1999 Mar 19;96(6):795-806, and Liang Y., et al., J. Biol. Chem. 1999 Jun 18;274(25):17885-92). Slit gene products are secreted proteins that contain both EGF domain and Leucine Rich Repeat domains; and function as ligands for cell-surface receptors. In Drosophilia, Slits are important in the development of midline glia and commissural axon pathways. In vertebrates, Slit family proteins have been shown to function as ligands of receptors in nervous system tissue. Slit proteins are thought to be critical for certain stages of central nervous system histogenesis and to have evolutionarily conserved roles in axon guidance (Brose K., et al., Cell 1999 Mar 19;96(6):795-806 and Liang Y., et al., J. Biol. Chem. 1999 Jun 18;274(25):17885-92). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with Slit proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in human hippocampus.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neurological, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution within human hippocampus combined with the homology to the Drosophila slit protein, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: IPLTLPGIFLLIRLFWRLGQSICGPGKLVLWPQFCCGCAVISGHCVPRGMPSSW LPGCFVLLCLVAVGCQLREWGVGGVSAVGLLALPHLQVLGMRGRGLISGG (SEQ ID NO: 199). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

This gene is expressed in KMH2 cells, osteoblasts, fetal spleen, Jurkat membrane bound polysomes, breast, and cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, immune, and skeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, skeletal, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard

gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in KMH2 cells, osteoblasts, and fetal spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal spleen and T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with phospholipase A2 which cleaves fatty acids from carbon 2 of glycerol (ref. Prosite pattern documentation for PS2_HIS). Many snake venoms contain phospolipase A2, which prevents transmission of nerve impulses to muscles by blocking the release of acetylcholine from the neuron. Therefore, included in this invention as preferred domains are Phospholipase A2 histidine active site domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). Phospholipase A2 is an enzyme which releases fatty acids from the second carbon group of glycerol. Structurally, PA2's are small and rigid proteins of 120 amino-acid residues that have four to seven disulfide bonds. PA2 binds a calcium ion which is required for activity. The side chains of two conserved residues, a histidine and an aspartic acid, participate in a 'catalytic network'. Two different signature patterns for PA2's were developed. The first is centered on the active site histidine and contains three cysteines involved in disulfide bonds. The consensus pattern is as follows: C-C-x(2)-H-x(2)-C [H is the active site residue]. Preferred polypeptides of the invention comprise a Phospholipase A2 histidine active site domain selected from the following amino acid sequences: CCNQHDRC (SEQ ID NO: 201), SLTKCCNQHDRCYET (SEQ ID NO: 202) and/or LTKCCNQHDRCYETCG (SEQ ID NO: 203). Polynucleotides encoding these polypeptides are also encompassed by the invention. Further preferred are polypeptides comprising the Phospholipase A2 histidine active site domain of the sequence listed in Table 1A for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues may be N-terminal or C- terminal to the Phospholipase A2 histidine active site domain. Alternatively, the additional contiguous amino acid residues may be both N-terminal and C-terminal to the Phospholipase A2 histidine active site domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to Phospholipase A2 proteins. Based on the sequence similarity, the translation product of this clone is

expected to share at least some biological activities with Phospholipase A2 proteins. Such activities are known in the art, some of which are described elsewhere herein, or see, for example, McIntosh, et al. J. Biol. Chem. 270 (8), 3518-3526 (1995), incorporated herein by reference.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GPAGKEAWIWSWLLPSPGPAPLPSASWGLCGDAPRAAARGPVEPGAARMAL LSRPALTLLLLLMAAVVRCQEQAQTTDWRATLKTIRNGVHKIDTYLNAALDL LGGEDGLCQYKCSDGSKPFPRYGYKPSPPNGCGSPLFGXHLNIGIPSLTKCCN QHDRCYETCGKSKNDCDEE FQYCLSKICRDVQKTLGLTQHVQACETTVELLFDSVIHLGCKPYLDSQRAAC RCHYEEKTDL (SEQ ID NO: 200). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed in a diverse variety of cell types.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, or metabolism disorders, specifically phospholipase A2 deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the neuromuscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pancreas, cancerous and wounded tissues) or bodily fluids (e.g., bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 108 as residues: Gln-23 to Asp-30, Lys-66 to Cys-87. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The ubiquitous tissue distribution and homology to phospholipase A2 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neuromuscular disorders. Alternatively, considering the activity of phospholipase A2 as a block for neuro- transmission may suggest that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

Alternatively, the homology to Phospholipase A2 proteins may indicate a potential use for the protein product of this clone in diagnosis, treatment and/or prevention of metabolism disorders, specifically deficiencies in Phospholipase A2. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GTSSARPRGALPGGSAPSAPHGQLPGRAQPAPVSGPPPTSGLCHFDPAAPWPL WPGPWQLPPHPQDWPAHPDIPQDWVSFLRSFGQLTLCPRNGTVTGKWRGSH VVGLLTTLNFGDGPDRNKTRTFQATVLGSQMGLKGSSAGQLVLITARVTTER TAGTCLYFSAVPGILPSSQPPISCSEEGAGNATLSPRMGEECVSVWSHEGLVLT KLLTSEELALCGSRLLVLGSFLLLFCGLLCCVTAMCFHPRRESHWSRTRL (SEQ ID NO: 204). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: ARAPPGPEGLSPEAQPPLLPMGNCQAGHNLHLCLAHHPPLVCATLILLLLGLS GLGLGSFLLTHRTGLRT LTSPRTGSLF (SEQ ID NO: 205). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the

invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in a wide variety of tissue types including testes, cerebellum, dendritic cells, breast cancer, umbilical vein endothelial cells, epididymus, corpus colosum, chronic synovitis, liver hepatoma, normal breast, osteoblasts, melanocytes, B cell lymphomas, and to a lesser extent in other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly of endothelial tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 109 as residues: Thr-52 to Gly-57. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that the protein product of this clone may play a role in the regulation of cellular division and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages.

In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also relies on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: RFLSVXPQXEVPFLLHPCVCFXGGHPSLLPDPCRAVGGGWEAPRCCLHEALC

QSLGCKAEEIVSVSESSSAQRCWYLLRGRKAGGRGPASPVLFALMRLESLCH LCLACLFFRLPATRTVYCMNEAEIVDVALGILIESRKQXKACEQPALAGADNP EHSPPCSVSPHTSSGSSSEEEDSGKQALXPGLSPSQRPGGSSSACSRSPEEEE EEDVLKYVREIFFS (SEQ ID NO: 206). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides of the invention do not consist of the nucleic acid sequences shown as GeneSeq Accession Nos: V59595 and V59744, which are hereby incorporated herein by reference.

This gene is expressed primarily in a variety of immune cell types, including stromal cells, dendritic cells, leukocytes, activated T-cells, macrophages, monocytes, neutrophils and to a lesser extent in a variety of other adult and fetal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in immune cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in fetal tissue and various hematopoietic cancers indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the NF-kB (Nuclear Factor kB) pathway. Thus, it is likely that this gene activates T-cells through the NF-kB signal transduction pathway. NF-kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity. In a specific embodiment polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

VPGWPRACSPCQADSPRAHPPKLRGILRWAPVPLXCAALCPPLDSGMSMAA CPEAPEPSFLREVPSSPASTQWHRPCNFRQVEANPRKEPKNLVWRDVSLGQX SRTPRGSGLELVRVCGGGMQRDKTVVEERVGEERERERERESLGGAGKHGE MRCVYVRESVGAPGRAGGGGNGVNSVGCVRTVHSGSXPPPSAGVS (SEQ ID NO: 207). Also preferred are the polynucleotides encoding these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in parts of the brain such as cerebellum and frontal lobe.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g., neural, cancerous, or wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in cerebellum and frontal lobe indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, prevention and/or treatment of neurodegenerative disease states and behavioural disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: TRPGKELNLVFGLQLSMARIGSTVNMNLMGWLYSKIEALLGSAGHTTLGITL MIGGITCILSLICALALA YLDQRAERILHKEQGKTGEVIKLTDVKDFSLPLWLIFIICVCYYVAVFPFIGLG KVFFTEKFGFSSQAAS AINSVVYVISAPMSPVFGLLVDKTGKNIIWVLCA (SEQ ID NO: 208). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in fetal tissue, and to a lesser extent in a variety of adult human tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fetal abnormalities, particularly developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 112 as residues: Lys-30 to Thr-35. Polynucleotides encoding said polypeptides are also

encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in fetal tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The translation product of this gene shares sequence homology with human histiocyte-secreted factor (HSF) which is a novel cytokine that shows in vivo antitumour activity without the cytotoxicity associated with tumor necrosis factor. Furthermore, the translation product of this gene also shares sequence homology with the human endogenous virus S71 gag polyprotein, the sequence of which is believed to represent a transformation locus for several cancers (See Genbank Accession No. pir|A46312|A46312; all references available through this accession are hereby incorporated by reference herein). Similarly, the translation product of this clone also shares homology with B219, a sequence that is expressed in at least four isoforms in very primitive hematopoietic cell populations which may represent a novel hemopoietin receptor (See, e.g., Cioffi, et al. Nat. Med. 2:585-589 (1996), which is hereby incorporated by reference herein).

In a preferred embodiment polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: CKDLCSRVYLLTLSPLLSYDPATSHSPRNTQ (SEQ ID NO: 209). Also preferred are the polynucleotides encoding these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in tonsil, and colon, and to a lesser extent in a wide variety of human tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and gastrointestinal disorders, particularly tumors of the colon and tonsil. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic, digestive and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, gastrointestinal, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 113 as residues: Met-1 to Cys-6. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in tonsil and colon, combined with the homology to human histiocyte growth factor, the human endogenous viral protein, and B219 strongly indicate that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment and/or prevention, of a variety of hematopoietic and immune system disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including

arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
IICECWEEECQSCRLKITQPREICRMDFLVLFLFYLASVLMGLVLICVCSKTHS
LKGLARGGAQIFSCIIPECLQRAXHGLLHYLFHTRNHTFIVLHLVLQGMVYTE
YTWEVFGYCQELELSLHYLLLPYLLLGVNLFFFTLTCGTNPGIITKANELLFLH
VYEFDEVMFPKNVRCSTCDLRKPARSKHCSVCNWCVHRFDHHCVWVNNCI
GAWNIRYFLIYVLTLTASAATVAIVSTTFLVHLVVMSDLYQETYIDDLGHLHV

MDTVFLIQYLFLTFPRIVFMLGFVVVLSFLLGGYLLFVLYLAATNQTTNEWYR GDWAWCQRCPLVAWPPSAEPQVHRNIHSHGLRSNLQEIFLPAFPCHERKKQE (SEQ ID NO: 210). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in colon and brain and to some extent in all tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and digestive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neurological, gastrointestinal, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not

limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternatively, expression of this gene in colon may indicate a role in the detection, prevention and/or treatment of colon disorders such as colon cancer, Crohn's disease, ulcers, and digestive tract disorders in general. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

When tested against Reh cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates B-cells through the Jaks-STAT signal transduction pathway. GAS isa promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene maps to chromosome 7, and therefore, may be used as a marker in linkage analysis for chromosome 7.

This gene is expressed primarily in brain, and in the developing embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, behavioral, immune, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developing, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 115 as residues: Lys-60 to Asn-67. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive

compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the tissue distribution in developing embryo indicates that the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

Alternatively, the biological activity within B-cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Activation of genes within B-cells indicates a role for this protein in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

This gene maps to chromosome 6, and therefore, may be used as a marker in linkage analysis for chromosome 6.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention

comprise, or alternatively consists of, the following amino acid sequence: LLSFKIRGLRTEDAGWAQSSSGGLCVRGDAFWMPSSSSGLGSPSRPPSSFLCL LLLLLP PAALALLLFFLDFFPPRAAVSPFLPDHCSARQPRVWRRETLNRSASGLGCWA RSTEQGAVGVATGTVLDI SLPASCLSLWPPGPSGGI (SEQ ID NO: 211). Polynucleotides encoding these polypeptides are also encompassed by the invention.

In a specific embodiment polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: QLGLCLTSASLPPASRCGHQAPLGASDLSAHHSAPGFSDSYFTMSCQSSLSRA EILQCPLVPSVSPPTHLPQGRANKSSRASLPLLPQTHWCLFPSARGWRRGIQSG LPPGGSCTSPRSPPQTLHQHITLVNHNTSYWQSPST (SEQ ID NO: 212), HQPPCLLPLAVATRPLWGHLTCLPIILHLVSVTLTSPCLANQAFQGQRSYNAL WCPLFLLLPTSPKGEQTNHPEPACPCFPKLTGVFSLQHVVGAEEFSQVFLLVD PVPVLDHLLKLFTSTSHLLIIIPHIGKAPAPDSLL EELSLSLATHCKVAVARFT (SEQ ID NO: 213). Also preferred are the polynucleotides encoding these polypeptides.

Polynucleotides of the invention do not consist of the nucleic acid sequence shown as GeneSeq Accession No. X04377, which is hereby incorporated herein by reference.

This gene is expressed primarily in brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, behavioral and neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 116 as residues: Pro-2 to Gly-7, Ser-10 to Ser-16, Pro-52 to Val-62, Arg-64 to Ser-73. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

The translation product of this gene was shown to have homology to the lysosomal mannosidase alpha-B protein (See Genbank Accession No. P34098) which is thought to be important in protein metabolism.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: MAAEGSRFSSQSPGLVDRQGPKCDPSRLVSPWGRHGLRILQIGHHHGRDGQH EATHHLLRVLRAPRVGKADEGAVDSDPSTPLQLKHEAAHAEDHAQQVHVVR RRVVQGRVTFARRGLVPQH FVRPPWVRHIVSGHSESKARSRLFRCRNRSFRRAS (SEQ ID NO: 214), and/or RLVSPWGRHGLRILQIGHHHGRDGQH EATHHLLRVLRA (SEQ ID NO: 215). An additional embodiment would be the polynucleotides encoding these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene maps to chromosome 19, and therefore, may be used as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in brain, placenta, fetal liver, and to a lesser extent in most tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, reproductive, and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, hepatic, or cancerous and wounded tissues) or bodily

fluids (e.g., bile, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 117 as residues: Asn-34 to Lys-42, Leu-60 to Trp-70. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution predominantly in brain indicates a role in the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Alternatively, the tissue distribution in liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

This gene is expressed primarily in spinal cord, Merkel cells, and adipose tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the nervous and immune systems, particularly those disorders relating to the CNS involving lipid metabolism disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of

the above tissues or cells, particularly of the nervous and immune systems and adipose tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spinal cord, Merkel cells and adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases the nervous systems, such as spinal cord injury, neurodegenerative diseases, muscular dystrophy or obesity. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

The translation product of this gene shares sequence homology with the human uncoupling protein-2 which is thought to be important in energy metabolism, obesity, and the predisposition of hyperinsulinemia (See Genbank Accession No. gi|1857278). Recently, another group published on this gene, designating it brain mitochondrial carrier protein-1 (BCMP1) (J Biol Chem 1998 Dec 18;273(51):34611-5).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: PTDVLKIRMQAQ (SEQ ID NO: 216), and/or TYEQLKR (SEQ ID NO: 217). An additional embodiment would be the polynucleotides encoding these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the

invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene maps to the X chromosome, and therefore, may be used as a marker in linkage analysis for the X chromosome.

This gene is expressed primarily in manic depression brain tissue, epileptic frontal cortex, human erythroleukemia cell line, T-helper cells, and to a lesser extent in endothelial and amygdala cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system or hematopoietic/immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system or hematopoietic/immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, hemolymphoid, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 119 as residues: Ser-34 to Thr-39, Gln-198 to Leu-205. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in neural tissues combined with the homology to the human uncoupling protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic

disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, given the homology to uncoupling proteins, the gene and/or its translation product may also be used in the diagnosis, treatment, and/or prevention of thermogenesis disorders such as obesity, cachexia, and hyperinsulinemia. Uncoupling proteins dissipate the proton gradient created from the oxidation of fuels by the electron transport chain, thus releasing stored energy as heat. Dysfunction of thermogenesis can induce disorders such as obesity and cachexia. It is thought that obesity may result from decreased thermogenesis in humans.

Alternatively, cachexia is a metabolic state in which energy expenditure exceeds food intake, for example in anorexia nervosa. Uncoupling proteins may be useful for the treatment and/or prevention of diseases and/or disorders involved with aberrant metabolic and thermogenic pathways. The following method provides for the determination of respiration uncoupling activity of the polypeptides of the present invention, including fragments and variants of the full length proteins. Briefly, yeast are transfected with an expression vector expressing polypeptide of the present invention as previously described by Bouillaud et al., EMBO J., 13:1990 (1994) (incorporated by reference herein in its entirety). Rates of growth in liquid medium of transformed yeast are measured in the presence of galactose, which induces expression, as described in International Publication No. WO 98/31396 (incorporated by reference herein in its entirety). Instantaneous generation times are compared between the polypeptide of the present invention and appropriate controls. An in vivo decrease of membrane potential associated with uncoupling of respiration is analyzed by flow cytometry of yeast labeled with the potential sensitive probe DiOC6 (3) (3,3'-dihexyloxacarbocyanine iodine, Molecular Probes, Eugene, OR). The ability of a polypeptide of the present invention to influence mitochondrial activity and uncouple respiration is thus determined.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

The translation product of this gene shares sequence homology with 55 kD deglycosylated zona pellucida protein which is known to be important in egg fertilization (See Genbank Accession No.R39356).

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: RPRPSASSLARSASLLPAAHGXGVGGAGGGSSXLRSRYQQLQNEEESGEPEQ AAGDAPPPYSSISAESAHXFDYKDESGFPKPPSYNVATTLPSYDEAERTKAEA TIPLVPGRDEDFVGRDDFDDADQLRIGNDGIF (SEQ ID NO: 218), RYQQLQNEEESGEPEQAAGD (SEQ ID NO: 219), and/or PGRDEDFVGRDDFDDADQLRIG (SEQ ID NO: 220). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

An additional embodiment would be the polynucleotides encoding these polypeptides. Preferred polypeptide fragments of the invention comprise, or alternatively consists of, the following amino acid sequence: MLTFFMAFLFNWIGFFLSFCLTTSAAGRYGAISGFGLSLIKWILIVRFSTYFPGY FDGQYWLWWVFLVLGFLLFLRGFINYAKVRKMPET FSNLPRTRVLFIY (SEQ ID NO: 221). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by

the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide variants of the invention comprise, or alternatively consists of, the following amino acid sequence:

MKKSLENLNRLQVMLLHLTAAFLQRAQHXFDYKDESGFPKPPSYNVATTLPS YDEAERTKAEATIPLVPGRDEDFVGRDDFDDADQLRIGNDGIFMLTFFMAFLF NWIGFFLSFCLTTSAAGRYGAISGFGLSLIKWILIVRFSTYFPGYFDGQYWLW WVFLVLGFLLFLRGFINYAKVR KMPETFSNLPRTRVLFIY (SEQ ID NO: 222), MLLHLTAAFLQRAQFSTYFPGYFDGQYWLWWVFLVLGFLLFLRGFINYAKV RKMPETFSN LPRTRVLFIY (SEQ ID NO: 223), MLTFFMAFLFNWIGFFLSFCLTTSAAGRYGAISGFGLSLIKWILIVRFSTYFPAF MNSLS RSKRTPAGSESRCRTQRNNHLL (SEQ ID NO: 224), and/or MKKSLENLNRLQVMLLHLTAAFLQRAHXIL TTRMSLGFQSPHLTM (SEQ ID NO: 225) . Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in adult kidney, colon adenocarcinoma, and fetal brain, and to a lesser extent, ubiquitously expression in many tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of kidney, colon cancers, and central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal and neural systems, and cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, neural, urogenital, or cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 120 as residues: Cys-15 to Gly-36. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution adult kidney, colon adenocarcinoma, and fetal brain indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of kidney diseases, colon cancers, and disorders of the central nervous system. Additionally, the homology to the zona pellucida protein indicates that the gene product may be used for male contraceptive development, and infertility diagnosis etc. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

The translation product of this gene shares sequence homology with the chicken transferrin receptor in addition to a human prostate-specific protein homolog (See Genbank Accession Nos.pir|JH0570|JH0570 and gi|2565338 (AF026380), respectively).

This gene also shares significant homology with both the murine and the rat hematopoietic lineage switch 2 proteins (See Genbank Accession Nos. g3169729 and g3851632, respectively), which are induced during an erythroid to myeloid lineage switch.

A preferred polypeptide fragment of the invention comprises, or alternatively consists of, the following amino acid sequence: MTVMDPKQMNVAAAVWAVVSYVVADMEEMLPRS (SEQ ID NO: 226). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal tissues, such as liver/spleen and brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pre-natal disorders, anomalies, deficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 121 as residues: Arg-31 to Lys-37, Lys-58 to Glu-65, Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of pre-natal disorders, anomalies and deficiencies. The homology to the hematopoietic lineage switch 2 proteins indicates that the translation product of this clone is useful for the detection and/or treatment of immune system disorders. In addition, the homology to the transferrin receptor indicates that the translation product of the present invention may have utility in the regulation of iron metabolism as well as the numerous genes under the stringent control of physiologic iron levels. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PRVRSREPVAGAPGCGTAGPPAMATLWGGLLRLGSLLSLSCLALSVLLLAHC
QTPPSDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLL
LYMVYLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANV
LNKVEYAQQRWKLQVQEQRKSVFDRHVVLS (SEQ ID NO: 227).
Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example,

fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 72 - 88 of the amino acid sequence referenced in Table 1A for this gene. Moreover, a cytoplasmic tail encompassing amino acids 89 to 167 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

A preferred polypeptide variant of the invention comprise, or alternatively consists of, the following amino acid sequence:
MATLWGGLLRLGSLLSLSCLALSVLLLAHCQTPPRISRMSDVNVSALPIKKNS
GHIYNKN ISQKDCDCLHVVEPMPVRGPDVEAYCLRCE
CKYEERSSVTIKVTIIIYLSILGLLLLYMV
YLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVE
YGTAALE
ASSPRAAKSLSLTGMLSSANWGIEFKVTRKKQADNWKGTDWVLLGFILIPC
(SEQ ID NO: 228). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in infant brain tissue, and to a lesser extent in other cell types and tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and neurodegenerative diseases of the brain and nervous system, such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, mania, dementia, paranoia, addictive behavior, sleep disorders, epilepsy, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 122 as residues: Gln-110 to Pro-120, Val-152 to Val-159. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of developmental, degenerative and behavioral conditions of the brain and nervous system. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette Syndrome, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), mania, depression, dementia, paranoia, addictive behavior, obsessive-compulsive disorder and sleep

disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 20

The translation product of this gene shares sequence homology with a recently published gene Dysferlin, which is thought to be a skeletal muscle gene that is mutated in Miyoshi myopathy and limb girdle muscular dystrophy (See Genbank Accession No. g3600028, and Nat. Genet. 20 (1), 31-36 (1998)).

This gene is expressed primarily in fetal liver, fetal heart tissue, and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunodeficiency, tumor necrosis, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and liver disorders, vascular disorders, and cancers (e.g., hepatoblastoma, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, developmental, vascular, or cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, bile, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune

disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-supressive conditions (transplantation) and hematopoeitic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Expression in liver may suggest a role for this gene product in the treatment and detection of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Alternatively, the tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stoke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Additionally, the homology to the dysferlin gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diseases related to degenerative myopathies that are characterized by the weakness and atrophy of muscles without neural degradation; such as Duchenne and Becker's muscular dystropies. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in haemopoietic cells and tumor cells, such as pancreatic tumor tissue, and to a lesser extent in bladder cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, haemopoietic disorders, diseases of the renal and pancreatic systems, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

haemopoietic, pancreatic, and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pancreas, renal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the renal, pancreatic and haemopoietic systems, and cancers thereof. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene is expressed primarily in liver tissue, cancer cells and fetal lung tissue, and to a lesser extent in dendritic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders, diseases of developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus, metabolic systems and cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing, metabolic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 125 as residues: His-44 to Gly-49. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the fetus, metabolic systems and cancers. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

This gene is expressed primarily in central nervous system tissues and cancers, such as endometrial tumors, and to a lesser extent in other tissues and organs.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the CNS and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and cancerous tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or

another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 126 as residues: Tyr-16 to Ser-22, Asp-209 to Leu-215. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in endometrial tumors. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

The translation product of this gene shares sequence homology with low-density lipoprotein receptor (See Genbank Accession No. >dbj|BAA24580.1), which is thought to be important in the pathogenesis of atherosclerosis and other disorders. The translation product of this gene also shares sequence homology with a rat homolog of the human CD94 (See Genbank Accession No. gb|AAC10220.1).

This gene is expressed primarily in macrophages, eosinophils, neutrophil and other cells of the haemopoietic and immune system.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune and haemopoietic systems and diseases of the endothelial and vascular system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, haemopoietic and vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 127 as residues: Lys-9 to Ala-17, Met-55 to Leu-61, Tyr-105 to Cys-127, Asp-132 to Lys-141, Ser-165 to Tyr-172, Pro-178 to Met-186, His-222 to Gln-227. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution and homology to LDL receptor and rat CD94 homolog indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the immune, haemopoietic and vascular systems. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. Expression of this gene product in eosinophils and macrophage also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 25

This gene is expressed primarily in infant brain and placental tissues, and to a lesser extent in several other tissues including immune and cancers.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 128 as residues: Leu-56 to Thr-62, Gln-80 to Pro-87, Gly-106 to Gln-113, Pro-122 to Lys-127, Gln-138 to Asn-146, Cys-280 to Lys-287, Asp-306 to Gly-311, Asp-321 to Thr-326, Gly-337 to Pro-345, Thr-354 to Gln-359, Asn-451 to Ile-457, Lys-526 to Glu-532, and Gln-591 to Glu-603. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

In a specific embodiment, polypeptides of the invention, comprise or alternatively consist of, one or more of the following amino acid sequences: MAAAGRLPSSWALFSPLLAGLALLGVGPVPARALHNVTAELFGAEAWGTLA AFGDLNSDKQTDLFVLRERNDLIVFLADQNAPYFKPKVKVSFKNHSALITSVV PGDYDGDSQMDVLLTYLPKNYAKSELGAVIFWGQNQTLDPNNMTILNRTFQ DEPLIMDFNGDLIPDIFGITNESNQPQILLGGNLSWHPALTTTSKMRIPHSHAFI DLTEDFTADLFLTTLNATTSTFQFEIWENLDGNFSVSTILEKPQNMMVVGQSA FADFDGDGHMDHLLPGCEDKNCQKSTIYLVRSGMKQWVPVLQDFSNKGTL WGFVPFVDEQQPTEIPIPITLHIGDYNMDGYPDALVILKNTSGSNQQAFLLENV PCNNASCEEARRMFKVYWELTDLNQIKDAMVATFFDIYEDGILDIVVLSKGY TKNDFAIHTLKNNFEADAYFVKVIVLSGLCSNDCPRR (SEQ ID NO: 227). Polynucleotides encoding these polypeptides are also encompassed by the invention as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention.

Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also preferred are polypeptides, comprising or alternatively consisting of, the mature polypeptide which is predicted to consist of residues 34-612 of the foregoing sequence (SEQ ID NO:128), and biologically active fragments of the mature polypeptide (e.g., fragments that induce secretion of IFNγ). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Figures 1A-C show the nucleotide (SEQ ID NO:35) and deduced amino acid sequence (SEQ ID NO:128) corresponding to this gene.

Figure 2 shows an analysis of the amino acid sequence (SEQ ID NO:128). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

The data presented in Figure 2 are also represented in tabular form in Table 6. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 2, and Table 6: "Res": amino acid residue of SEQ ID NO:128 and Figures 1A – 1C; "Position": position of the corresponding residue within SEQ ID NO:128 and Figures 1A - 1C; I: Alpha, Regions - Garnier-Robson;

II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 2 and/or Table 6, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 6 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 2, but may, as shown in Table 6, be represented or identified by using tabular representations of the data presented in Figure 2. The DNA*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 2 in a tabular format (See Table 6). The tabular format of the data in Figure 2 is used to easily determine specific boundaries of a preferred region.

The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 35,

is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:35. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:35. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150 from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1400, from about 1401 to about 1450, and from about 1451 to about 1500, from about 1501 to about 1550, from about 1551 to about 1600, from about 1601 to about 1650 from about 1651 to about 1700, from about 1701 to about 1750, from about 1751 to about 1800, from about 1801 to about 1850, from about 1851 to about 1900, from about 1901 to about 1950, and from about 1951 to about 2000,

from about 2001 to about 2050, from about 2051 to about 2100, from about 2101 to about 2150, from about 2151 to about 2200, from about 2201 to about 2250, or from about 2251 to about 2312 of SEQ ID NO:35, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-612 where m is an integer from 2 to 606, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:128. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: A-2 to M-612; A-3 to M-612; A-4 to M-612; G-5 to M-612; R-6 to M-612; L-7 to M-612; P-8 to M-612; S-9 to M-612; S-10 to M-612; W-11 to M-612; A-12 to M-612; L-13 to M-612; F-14 to M-612; S-15 to M-612; P-16 to M-612; L-17 to M-612; L-18 to M-612; A-19 to M-612; G-20 to M-612; L-21 to M-612; A-22 to M-612; L-23 to M-612; L-24 to M-612; G-25 to M-612; V-26 to M-612; G-27 to M-612; P-28 to M-612; V-29 to M-612; P-30 to M-612; A-31 to M-612; R-32 to M-612; A-33 to M-612; L-34 to M-612; H-35 to M-612; N-36 to M-612; V-37 to M-612; T-38 to M-612; A-39 to M-612; E-40 to M-612; L-41 to M-612; F-42 to M-612; G-43 to M-612; A-44 to M-612; E-45 to M-612; A-46 to M-612; W-47 to M-612; G-48 to M-612; T-49 to M-612; L-50 to M-612; A-51 to M-612; A-52 to M-612; F-53 to M-612; G-54 to M-612; D-55 to M-612; L-56 to M-612; N-57 to M-612; S-58 to M-612; D-59 to M-612; K-60 to M-612; Q-61 to M-612; T-62 to M-612; D-63 to M-612; L-64 to M-612; F-65 to M-612; V-66 to M-612; L-67 to M-612; R-68 to M-612; E-69 to M-612; R-70 to M-612; N-71 to M-612; D-72 to M-612; L-73 to M-612; I-74 to M-612; V-75 to M-612; F-76 to M-612; L-77 to M-612; A-78 to M-612; D-79 to M-612; Q-80 to M-612; N-81 to M-612; A-82 to M-612; P-83 to M-612; Y-84 to M-612; F-85 to M-612; K-86 to M-612; P-87 to M-612; K-88

to M-612; V-89 to M-612; K-90 to M-612; V-91 to M-612; S-92 to M-612; F-93 to M-612; K-94 to M-612; N-95 to M-612; H-96 to M-612; S-97 to M-612; A-98 to M-612; L-99 to M-612; I-100 to M-612; T-101 to M-612; S-102 to M-612; V-103 to M-612; V-104 to M-612; P-105 to M-612; G-106 to M-612; D-107 to M-612; Y-108 to M-612; D-109 to M-612; G-110 to M-612; D-111 to M-612; S-112 to M-612; Q-113 to M-612; M-114 to M-612; D-115 to M-612; V-116 to M-612; L-117 to M-612; L-118 to M-612; T-119 to M-612; Y-120 to M-612; L-121 to M-612; P-122 to M-612; K-123 to M-612; N-124 to M-612; Y-125 to M-612; A-126 to M-612; K-127 to M-612; S-128 to M-612; E-129 to M-612; L-130 to M-612; G-131 to M-612; A-132 to M-612; V-133 to M-612; I-134 to M-612; F-135 to M-612; W-136 to M-612; G-137 to M-612; Q-138 to M-612; N-139 to M-612; Q-140 to M-612; T-141 to M-612; L-142 to M-612; D-143 to M-612; P-144 to M-612; N-145 to M-612; N-146 to M-612; M-147 to M-612; T-148 to M-612; I-149 to M-612; L-150 to M-612; N-151 to M-612; R-152 to M-612; T-153 to M-612; F-154 to M-612; Q-155 to M-612; D-156 to M-612; E-157 to M-612; P-158 to M-612; L-159 to M-612; I-160 to M-612; M-161 to M-612; D-162 to M-612; F-163 to M-612; N-164 to M-612; G-165 to M-612; D-166 to M-612; L-167 to M-612; I-168 to M-612; P-169 to M-612; D-170 to M-612; I-171 to M-612; F-172 to M-612; G-173 to M-612; I-174 to M-612; T-175 to M-612; N-176 to M-612; E-177 to M-612; S-178 to M-612; N-179 to M-612; Q-180 to M-612; P-181 to M-612; Q-182 to M-612; I-183 to M-612; L-184 to M-612; L-185 to M-612; G-186 to M-612; G-187 to M-612; N-188 to M-612; L-189 to M-612; S-190 to M-612; W-191 to M-612; H-192 to M-612; P-193 to M-612; A-194 to M-612; L-195 to M-612; T-196 to M-612; T-197 to M-612; T-198 to M-612; S-199 to M-612; K-200 to M-612; M-201 to M-612; R-202 to M-612; I-203 to M-612; P-204 to M-612; H-205 to M-612; S-206 to M-612; H-207 to M-612; A-208 to M-612; F-209 to M-612; I-210 to M-612; D-211 to M-612; L-212 to M-612; T-213 to M-612; E-214 to M-612; D-215 to M-612; F-216 to M-612; T-217 to M-612; A-218 to M-612; D-219 to M-612; L-220 to M-612; F-221 to M-612; L-222 to M-612; T-223 to M-612; T-224 to M-612; L-225 to M-612; N-226 to M-612; A-227 to M-612; T-228 to M-612; T-229 to M-612; S-230 to M-612; T-231 to M-612; F-232 to M-612; Q-233 to M-612; F-234 to M-612; E-235 to M-612; I-236 to M-612; W-237 to M-612; E-238 to M-612; N-239 to M-612; L-240 to M-612; D-241 to M-612; G-242 to M-612; N-243 to M-612;

F-244 to M-612; S-245 to M-612; V-246 to M-612; S-247 to M-612; T-248 to M-612; I-249 to M-612; L-250 to M-612; E-251 to M-612; K-252 to M-612; P-253 to M-612; Q-254 to M-612; N-255 to M-612; M-256 to M-612; M-257 to M-612; V-258 to M-612; V-259 to M-612; G-260 to M-612; Q-261 to M-612; S-262 to M-612; A-263 to M-612; F-264 to M-612; A-265 to M-612; D-266 to M-612; F-267 to M-612; D-268 to M-612; G-269 to M-612; D-270 to M-612; G-271 to M-612; H-272 to M-612; M-273 to M-612; D-274 to M-612; H-275 to M-612; L-276 to M-612; L-277 to M-612; P-278 to M-612; G-279 to M-612; C-280 to M-612; E-281 to M-612; D-282 to M-612; K-283 to M-612; N-284 to M-612; C-285 to M-612; Q-286 to M-612; K-287 to M-612; S-288 to M-612; T-289 to M-612; I-290 to M-612; Y-291 to M-612; L-292 to M-612; V-293 to M-612; R-294 to M-612; S-295 to M-612; G-296 to M-612; M-297 to M-612; K-298 to M-612; Q-299 to M-612; W-300 to M-612; V-301 to M-612; P-302 to M-612; V-303 to M-612; L-304 to M-612; Q-305 to M-612; D-306 to M-612; F-307 to M-612; S-308 to M-612; N-309 to M-612; K-310 to M-612; G-311 to M-612; T-312 to M-612; L-313 to M-612; W-314 to M-612; G-315 to M-612; F-316 to M-612; V-317 to M-612; P-318 to M-612; F-319 to M-612; V-320 to M-612; D-321 to M-612; E-322 to M-612; Q-323 to M-612; Q-324 to M-612; P-325 to M-612; T-326 to M-612; E-327 to M-612; I-328 to M-612; P-329 to M-612; I-330 to M-612; P-331 to M-612; I-332 to M-612; T-333 to M-612; L-334 to M-612; H-335 to M-612; I-336 to M-612; G-337 to M-612; D-338 to M-612; Y-339 to M-612; N-340 to M-612; M-341 to M-612; D-342 to M-612; G-343 to M-612; Y-344 to M-612; P-345 to M-612; D-346 to M-612; A-347 to M-612; L-348 to M-612; V-349 to M-612; I-350 to M-612; L-351 to M-612; K-352 to M-612; N-353 to M-612; T-354 to M-612; S-355 to M-612; G-356 to M-612; S-357 to M-612; N-358 to M-612; Q-359 to M-612; Q-360 to M-612; A-361 to M-612; F-362 to M-612; L-363 to M-612; L-364 to M-612; E-365 to M-612; N-366 to M-612; V-367 to M-612; P-368 to M-612; C-369 to M-612; N-370 to M-612; N-371 to M-612; A-372 to M-612; S-373 to M-612; C-374 to M-612; E-375 to M-612; E-376 to M-612; A-377 to M-612; R-378 to M-612; R-379 to M-612; M-380 to M-612; F-381 to M-612; K-382 to M-612; V-383 to M-612; Y-384 to M-612; W-385 to M-612; E-386 to M-612; L-387 to M-612; T-388 to M-612; D-389 to M-612; L-390 to M-612; N-391 to M-612; Q-392 to M-612; I-393 to M-612; K-394 to M-612; D-395 to M-612; A-396 to M-612; M-397 to M-612; V-398 to

M-612; A-399 to M-612; T-400 to M-612; F-401 to M-612; F-402 to M-612; D-403 to M-612; I-404 to M-612; Y-405 to M-612; E-406 to M-612; D-407 to M-612; G-408 to M-612; I-409 to M-612; L-410 to M-612; D-411 to M-612; I-412 to M-612; V-413 to M-612; V-414 to M-612; L-415 to M-612; S-416 to M-612; K-417 to M-612; G-418 to M-612; Y-419 to M-612; T-420 to M-612; K-421 to M-612; N-422 to M-612; D-423 to M-612; F-424 to M-612; A-425 to M-612; I-426 to M-612; H-427 to M-612; T-428 to M-612; L-429 to M-612; K-430 to M-612; N-431 to M-612; N-432 to M-612; F-433 to M-612; E-434 to M-612; A-435 to M-612; D-436 to M-612; A-437 to M-612; Y-438 to M-612; F-439 to M-612; V-440 to M-612; K-441 to M-612; V-442 to M-612; I-443 to M-612; V-444 to M-612; L-445 to M-612; S-446 to M-612; G-447 to M-612; L-448 to M-612; C-449 to M-612; S-450 to M-612; N-451 to M-612; D-452 to M-612; C-453 to M-612; P-454 to M-612; R-455 to M-612; K-456 to M-612; I-457 to M-612; T-458 to M-612; P-459 to M-612; F-460 to M-612; G-461 to M-612; V-462 to M-612; N-463 to M-612; Q-464 to M-612; P-465 to M-612; G-466 to M-612; P-467 to M-612; Y-468 to M-612; I-469 to M-612; M-470 to M-612; Y-471 to M-612; T-472 to M-612; T-473 to M-612; V-474 to M-612; D-475 to M-612; A-476 to M-612; N-477 to M-612; G-478 to M-612; Y-479 to M-612; L-480 to M-612; K-481 to M-612; N-482 to M-612; G-483 to M-612; S-484 to M-612; A-485 to M-612; G-486 to M-612; Q-487 to M-612; L-488 to M-612; S-489 to M-612; Q-490 to M-612; S-491 to M-612; A-492 to M-612; H-493 to M-612; L-494 to M-612; A-495 to M-612; L-496 to M-612; Q-497 to M-612; L-498 to M-612; P-499 to M-612; Y-500 to M-612; N-501 to M-612; V-502 to M-612; L-503 to M-612; G-504 to M-612; L-505 to M-612; G-506 to M-612; R-507 to M-612; S-508 to M-612; A-509 to M-612; N-510 to M-612; F-511 to M-612; L-512 to M-612; D-513 to M-612; H-514 to M-612; L-515 to M-612; Y-516 to M-612; V-517 to M-612; G-518 to M-612; I-519 to M-612; P-520 to M-612; R-521 to M-612; P-522 to M-612; S-523 to M-612; G-524 to M-612; E-525 to M-612; K-526 to M-612; S-527 to M-612; I-528 to M-612; R-529 to M-612; K-530 to M-612; Q-531 to M-612; E-532 to M-612; W-533 to M-612; T-534 to M-612; A-535 to M-612; I-536 to M-612; I-537 to M-612; P-538 to M-612; N-539 to M-612; S-540 to M-612; Q-541 to M-612; L-542 to M-612; I-543 to M-612; V-544 to M-612; I-545 to M-612; P-546 to M-612; Y-547 to M-612; P-548 to M-612; H-549 to M-612; N-550 to M-612; V-551 to M-612; P-552 to M-612; R-553

to M-612; S-554 to M-612; W-555 to M-612; S-556 to M-612; A-557 to M-612; K-558 to M-612; L-559 to M-612; Y-560 to M-612; L-561 to M-612; T-562 to M-612; P-563 to M-612; S-564 to M-612; N-565 to M-612; I-566 to M-612; V-567 to M-612; L-568 to M-612; L-569 to M-612; T-570 to M-612; A-571 to M-612; I-572 to M-612; A-573 to M-612; L-574 to M-612; I-575 to M-612; G-576 to M-612; V-577 to M-612; C-578 to M-612; V-579 to M-612; F-580 to M-612; I-581 to M-612; L-582 to M-612; A-583 to M-612; I-584 to M-612; I-585 to M-612; G-586 to M-612; I-587 to M-612; L-588 to M-612; H-589 to M-612; W-590 to M-612; Q-591 to M-612; E-592 to M-612; K-593 to M-612; K-594 to M-612; A-595 to M-612; D-596 to M-612; D-597 to M-612; R-598 to M-612; E-599 to M-612; K-600 to M-612; R-601 to M-612; Q-602 to M-612; E-603 to M-612; A-604 to M-612; H-605 to M-612; R-606 to M-612; and F-607 to M-612 of SEQ ID NO: 128. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to induce IFN gamma production), other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a

large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 1A-C (SEQ ID NO:128), as described by the general formula 1-n, where n is an integer from 6 to 611, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:128. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: M-1 to A-611; M-1 to D-610; M-1 to F-609; M-1 to H-608; M-1 to F-607; M-1 to R-606; M-1 to H-605; M-1 to A-604; M-1 to E-603; M-1 to Q-602; M-1 to R-601; M-1 to K-600; M-1 to E-599; M-1 to R-598; M-1 to D-597; M-1 to D-596; M-1 to A-595; M-1 to K-594; M-1 to K-593; M-1 to E-592; M-1 to Q-591; M-1 to W-590; M-1 to H-589; M-1 to L-588; M-1 to I-587; M-1 to G-586; M-1 to I-585; M-1 to I-584; M-1 to A-583; M-1 to L-582; M-1 to I-581; M-1 to F-580; M-1 to V-579; M-1 to C-578; M-1 to V-577; M-1 to G-576; M-1 to I-575; M-1 to L-574; M-1 to A-573; M-1 to I-572; M-1 to A-571; M-1 to T-570; M-1 to L-569; M-1 to L-568; M-1 to V-567; M-1 to I-566; M-1 to N-565; M-1 to S-564; M-1 to P-563; M-1 to T-562; M-1 to L-561; M-1 to Y-560; M-1 to L-559; M-1 to K-558; M-1 to A-557; M-1 to S-556; M-1 to W-555; M-1 to S-554; M-1 to R-553; M-1 to P-552; M-1 to V-551; M-1 to N-550; M-1 to H-549; M-1 to P-548; M-1 to Y-547; M-1 to P-546; M-1 to I-545; M-1 to V-544; M-1 to I-543; M-1 to L-542; M-1 to Q-541; M-1 to S-540; M-1 to N-539; M-1 to P-538; M-1 to I-537; M-1 to I-536; M-1 to A-535; M-1 to T-534; M-1 to W-533; M-1 to E-532; M-1 to Q-531; M-1 to K-530; M-1 to R-529; M-1 to I-528; M-1 to S-527; M-1 to K-526; M-1 to E-525; M-1 to G-524; M-1 to S-523; M-1 to P-522; M-1 to R-521; M-1 to P-520; M-1 to I-519; M-1 to G-518; M-1 to V-517; M-1 to Y-516; M-1 to L-515; M-1 to H-514; M-1 to D-513; M-1 to L-512; M-1 to F-511; M-1 to N-510; M-1 to A-509; M-1 to S-508; M-1 to R-507; M-1 to G-506; M-1 to L-505; M-1 to G-504; M-1 to L-503; M-1 to V-502; M-1 to N-501; M-1 to Y-500; M-1 to P-499; M-1 to L-498; M-1 to Q-497; M-1 to L-496; M-1 to A-495; M-1 to L-494; M-1 to H-493; M-1 to A-492; M-1 to S-491; M-1 to Q-490; M-1 to S-489; M-1 to L-488; M-1 to Q-487; M-1

to G-486; M-1 to A-485; M-1 to S-484; M-1 to G-483; M-1 to N-482; M-1 to K-481; M-1 to L-480; M-1 to Y-479; M-1 to G-478; M-1 to N-477; M-1 to A-476; M-1 to D-475; M-1 to V-474; M-1 to T-473; M-1 to T-472; M-1 to Y-471; M-1 to M-470; M-1 to I-469; M-1 to Y-468; M-1 to P-467; M-1 to G-466; M-1 to P-465; M-1 to Q-464; M-1 to N-463; M-1 to V-462; M-1 to G-461; M-1 to F-460; M-1 to P-459; M-1 to T-458; M-1 to I-457; M-1 to K-456; M-1 to R-455; M-1 to P-454; M-1 to C-453; M-1 to D-452; M-1 to N-451; M-1 to S-450; M-1 to C-449; M-1 to L-448; M-1 to G-447; M-1 to S-446; M-1 to L-445; M-1 to V-444; M-1 to I-443; M-1 to V-442; M-1 to K-441; M-1 to V-440; M-1 to F-439; M-1 to Y-438; M-1 to A-437; M-1 to D-436; M-1 to A-435; M-1 to E-434; M-1 to F-433; M-1 to N-432; M-1 to N-431; M-1 to K-430; M-1 to L-429; M-1 to T-428; M-1 to H-427; M-1 to I-426; M-1 to A-425; M-1 to F-424; M-1 to D-423; M-1 to N-422; M-1 to K-421; M-1 to T-420; M-1 to Y-419; M-1 to G-418; M-1 to K-417; M-1 to S-416; M-1 to L-415; M-1 to V-414; M-1 to V-413; M-1 to I-412; M-1 to D-411; M-1 to L-410; M-1 to I-409; M-1 to G-408; M-1 to D-407; M-1 to E-406; M-1 to Y-405; M-1 to I-404; M-1 to D-403; M-1 to F-402; M-1 to F-401; M-1 to T-400; M-1 to A-399; M-1 to V-398; M-1 to M-397; M-1 to A-396; M-1 to D-395; M-1 to K-394; M-1 to I-393; M-1 to Q-392; M-1 to N-391; M-1 to L-390; M-1 to D-389; M-1 to T-388; M-1 to L-387; M-1 to E-386; M-1 to W-385; M-1 to Y-384; M-1 to V-383; M-1 to K-382; M-1 to F-381; M-1 to M-380; M-1 to R-379; M-1 to R-378; M-1 to A-377; M-1 to E-376; M-1 to E-375; M-1 to C-374; M-1 to S-373; M-1 to A-372; M-1 to N-371; M-1 to N-370; M-1 to C-369; M-1 to P-368; M-1 to V-367; M-1 to N-366; M-1 to E-365; M-1 to L-364; M-1 to L-363; M-1 to F-362; M-1 to A-361; M-1 to Q-360; M-1 to Q-359; M-1 to N-358; M-1 to S-357; M-1 to G-356; M-1 to S-355; M-1 to T-354; M-1 to N-353; M-1 to K-352; M-1 to L-351; M-1 to I-350; M-1 to V-349; M-1 to L-348; M-1 to A-347; M-1 to D-346; M-1 to P-345; M-1 to Y-344; M-1 to G-343; M-1 to D-342; M-1 to M-341; M-1 to N-340; M-1 to Y-339; M-1 to D-338; M-1 to G-337; M-1 to I-336; M-1 to H-335; M-1 to L-334; M-1 to T-333; M-1 to I-332; M-1 to P-331; M-1 to I-330; M-1 to P-329; M-1 to I-328; M-1 to E-327; M-1 to T-326; M-1 to P-325; M-1 to Q-324; M-1 to Q-323; M-1 to E-322; M-1 to D-321; M-1 to V-320; M-1 to F-319; M-1 to P-318; M-1 to V-317; M-1 to F-316; M-1 to G-315; M-1 to W-314; M-1 to L-313; M-1 to T-312; M-1 to G-311; M-1 to K-310; M-1 to N-309; M-1 to S-308; M-1 to F-307; M-1 to D-306; M-1 to Q-305; M-1

to L-304; M-1 to V-303; M-1 to P-302; M-1 to V-301; M-1 to W-300; M-1 to Q-299; M-1 to K-298; M-1 to M-297; M-1 to G-296; M-1 to S-295; M-1 to R-294; M-1 to V-293; M-1 to L-292; M-1 to Y-291; M-1 to I-290; M-1 to T-289; M-1 to S-288; M-1 to K-287; M-1 to Q-286; M-1 to C-285; M-1 to N-284; M-1 to K-283; M-1 to D-282; M-1 to E-281; M-1 to C-280; M-1 to G-279; M-1 to P-278; M-1 to L-277; M-1 to L-276; M-1 to H-275; M-1 to D-274; M-1 to M-273; M-1 to H-272; M-1 to G-271; M-1 to D-270; M-1 to G-269; M-1 to D-268; M-1 to F-267; M-1 to D-266; M-1 to A-265; M-1 to F-264; M-1 to A-263; M-1 to S-262; M-1 to Q-261; M-1 to G-260; M-1 to V-259; M-1 to V-258; M-1 to M-257; M-1 to M-256; M-1 to N-255; M-1 to Q-254; M-1 to P-253; M-1 to K-252; M-1 to E-251; M-1 to L-250; M-1 to I-249; M-1 to T-248; M-1 to S-247; M-1 to V-246; M-1 to S-245; M-1 to F-244; M-1 to N-243; M-1 to G-242; M-1 to D-241; M-1 to L-240; M-1 to N-239; M-1 to E-238; M-1 to W-237; M-1 to I-236; M-1 to E-235; M-1 to F-234; M-1 to Q-233; M-1 to F-232; M-1 to T-231; M-1 to S-230; M-1 to T-229; M-1 to T-228; M-1 to A-227; M-1 to N-226; M-1 to L-225; M-1 to T-224; M-1 to T-223; M-1 to L-222; M-1 to F-221; M-1 to L-220; M-1 to D-219; M-1 to A-218; M-1 to T-217; M-1 to F-216; M-1 to D-215; M-1 to E-214; M-1 to T-213; M-1 to L-212; M-1 to D-211; M-1 to I-210; M-1 to F-209; M-1 to A-208; M-1 to H-207; M-1 to S-206; M-1 to H-205; M-1 to P-204; M-1 to I-203; M-1 to R-202; M-1 to M-201; M-1 to K-200; M-1 to S-199; M-1 to T-198; M-1 to T-197; M-1 to T-196; M-1 to L-195; M-1 to A-194; M-1 to P-193; M-1 to H-192; M-1 to W-191; M-1 to S-190; M-1 to L-189; M-1 to N-188; M-1 to G-187; M-1 to G-186; M-1 to L-185; M-1 to L-184; M-1 to I-183; M-1 to Q-182; M-1 to P-181; M-1 to Q-180; M-1 to N-179; M-1 to S-178; M-1 to E-177; M-1 to N-176; M-1 to T-175; M-1 to I-174; M-1 to G-173; M-1 to F-172; M-1 to I-171; M-1 to D-170; M-1 to P-169; M-1 to I-168; M-1 to L-167; M-1 to D-166; M-1 to G-165; M-1 to N-164; M-1 to F-163; M-1 to D-162; M-1 to M-161; M-1 to I-160; M-1 to L-159; M-1 to P-158; M-1 to E-157; M-1 to D-156; M-1 to Q-155; M-1 to F-154; M-1 to T-153; M-1 to R-152; M-1 to N-151; M-1 to L-150; M-1 to I-149; M-1 to T-148; M-1 to M-147; M-1 to N-146; M-1 to N-145; M-1 to P-144; M-1 to D-143; M-1 to L-142; M-1 to T-141; M-1 to Q-140; M-1 to N-139; M-1 to Q-138; M-1 to G-137; M-1 to W-136; M-1 to F-135; M-1 to I-134; M-1 to V-133; M-1 to A-132; M-1 to G-131; M-1 to L-130; M-1 to E-129; M-1 to S-128; M-1 to K-127; M-1 to A-126; M-1 to Y-125; M-1 to N-124; M-1 to K-123;

M-1 to P-122; M-1 to L-121; M-1 to Y-120; M-1 to T-119; M-1 to L-118; M-1 to L-117; M-1 to V-116; M-1 to D-115; M-1 to M-114; M-1 to Q-113; M-1 to S-112; M-1 to D-111; M-1 to G-110; M-1 to D-109; M-1 to Y-108; M-1 to D-107; M-1 to G-106; M-1 to P-105; M-1 to V-104; M-1 to V-103; M-1 to S-102; M-1 to T-101; M-1 to I-100; M-1 to L-99; M-1 to A-98; M-1 to S-97; M-1 to H-96; M-1 to N-95; M-1 to K-94; M-1 to F-93; M-1 to S-92; M-1 to V-91; M-1 to K-90; M-1 to V-89; M-1 to K-88; M-1 to P-87; M-1 to K-86; M-1 to F-85; M-1 to Y-84; M-1 to P-83; M-1 to A-82; M-1 to N-81; M-1 to Q-80; M-1 to D-79; M-1 to A-78; M-1 to L-77; M-1 to F-76; M-1 to V-75; M-1 to I-74; M-1 to L-73; M-1 to D-72; M-1 to N-71; M-1 to R-70; M-1 to E-69; M-1 to R-68; M-1 to L-67; M-1 to V-66; M-1 to F-65; M-1 to L-64; M-1 to D-63; M-1 to T-62; M-1 to Q-61; M-1 to K-60; M-1 to D-59; M-1 to S-58; M-1 to N-57; M-1 to L-56; M-1 to D-55; M-1 to G-54; M-1 to F-53; M-1 to A-52; M-1 to A-51; M-1 to L-50; M-1 to T-49; M-1 to G-48; M-1 to W-47; M-1 to A-46; M-1 to E-45; M-1 to A-44; M-1 to G-43; M-1 to F-42; M-1 to L-41; M-1 to E-40; M-1 to A-39; M-1 to T-38; M-1 to V-37; M-1 to N-36; M-1 to H-35; M-1 to L-34; M-1 to A-33; M-1 to R-32; M-1 to A-31; M-1 to P-30; M-1 to V-29; M-1 to P-28; M-1 to G-27; M-1 to V-26; M-1 to G-25; M-1 to L-24; M-1 to L-23; M-1 to A-22; M-1 to L-21; M-1 to G-20; M-1 to A-19; M-1 to L-18; M-1 to L-17; M-1 to P-16; M-1 to S-15; M-1 to F-14; M-1 to L-13; M-1 to A-12; M-1 to W-11; M-1 to S-10; M-1 to S-9; M-1 to P-8; M-1 to L-7; and M-1 to R-6 of SEQ ID NO:128. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described

generally as having residues m-n of SEQ ID NO:128, where n and m are integers as described above. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: A-2 to K-558; A-3 to K-558; A-4 to K-558; G-5 to K-558; R-6 to K-558; L-7 to K-558; P-8 to K-558; S-9 to K-558; S-10 to K-558; W-11 to K-558; A-12 to K-558; L-13 to K-558; F-14 to K-558; S-15 to K-558; P-16 to K-558; L-17 to K-558; L-18 to K-558; A-19 to K-558; G-20 to K-558; L-21 to K-558; A-22 to K-558; L-23 to K-558; L-24 to K-558; G-25 to K-558; V-26 to K-558; G-27 to K-558; P-28 to K-558; V-29 to K-558; P-30 to K-558; A-31 to K-558; R-32 to K-558; A-33 to K-558; L-34 to K-558; H-35 to K-558; N-36 to K-558; V-37 to K-558; T-38 to K-558; A-39 to K-558; E-40 to K-558; L-41 to K-558; F-42 to K-558; G-43 to K-558; A-44 to K-558; E-45 to K-558; A-46 to K-558; W-47 to K-558; G-48 to K-558; T-49 to K-558; L-50 to K-558; A-51 to K-558; A-52 to K-558; F-53 to K-558; G-54 to K-558; D-55 to K-558; L-56 to K-558; N-57 to K-558; S-58 to K-558; D-59 to K-558; K-60 to K-558; Q-61 to K-558; T-62 to K-558; D-63 to K-558; L-64 to K-558; F-65 to K-558; V-66 to K-558; L-67 to K-558; R-68 to K-558; E-69 to K-558; R-70 to K-558; N-71 to K-558; D-72 to K-558; L-73 to K-558; I-74 to K-558; V-75 to K-558; F-76 to K-558; L-77 to K-558; A-78 to K-558; D-79 to K-558; Q-80 to K-558; N-81 to K-558; A-82 to K-558; P-83 to K-558; Y-84 to K-558; F-85 to K-558; K-86 to K-558; P-87 to K-558; K-88 to K-558; V-89 to K-558; K-90 to K-558; V-91 to K-558; S-92 to K-558; F-93 to K-558; K-94 to K-558; N-95 to K-558; H-96 to K-558; S-97 to K-558; A-98 to K-558; L-99 to K-558; I-100 to K-558; T-101 to K-558; S-102 to K-558; V-103 to K-558; V-104 to K-558; P-105 to K-558; G-106 to K-558; D-107 to K-558; Y-108 to K-558; D-109 to K-558; G-110 to K-558; D-111 to K-558; S-112 to K-558; Q-113 to K-558; M-114 to K-558; D-115 to K-558; V-116 to K-558; L-117 to K-558; L-118 to K-558; T-119 to K-558; Y-120 to K-558; L-121 to K-558; P-122 to K-558; K-123 to K-558; N-124 to K-558; Y-125 to K-558; A-126 to K-558; K-127 to K-558; S-128 to K-558; E-129 to K-558; L-130 to K-558; G-131 to K-558; A-132 to K-558; V-133 to K-558; I-134 to K-558; F-135 to K-558; W-136 to K-558; G-137 to K-558; Q-138 to K-558; N-139 to K-558; Q-140 to K-558; T-141 to K-558; L-142 to K-558; D-143 to K-558; P-144 to K-558; N-145 to K-558; N-146 to K-558; M-147 to K-558; T-148 to K-558; I-149 to K-558; L-150

to K-558; N-151 to K-558; R-152 to K-558; T-153 to K-558; F-154 to K-558; Q-155 to K-558; D-156 to K-558; E-157 to K-558; P-158 to K-558; L-159 to K-558; I-160 to K-558; M-161 to K-558; D-162 to K-558; F-163 to K-558; N-164 to K-558; G-165 to K-558; D-166 to K-558; L-167 to K-558; I-168 to K-558; P-169 to K-558; D-170 to K-558; I-171 to K-558; F-172 to K-558; G-173 to K-558; I-174 to K-558; T-175 to K-558; N-176 to K-558; E-177 to K-558; S-178 to K-558; N-179 to K-558; Q-180 to K-558; P-181 to K-558; Q-182 to K-558; I-183 to K-558; L-184 to K-558; L-185 to K-558; G-186 to K-558; G-187 to K-558; N-188 to K-558; L-189 to K-558; S-190 to K-558; W-191 to K-558; H-192 to K-558; P-193 to K-558; A-194 to K-558; L-195 to K-558; T-196 to K-558; T-197 to K-558; T-198 to K-558; S-199 to K-558; K-200 to K-558; M-201 to K-558; R-202 to K-558; I-203 to K-558; P-204 to K-558; H-205 to K-558; S-206 to K-558; H-207 to K-558; A-208 to K-558; F-209 to K-558; I-210 to K-558; D-211 to K-558; L-212 to K-558; T-213 to K-558; E-214 to K-558; D-215 to K-558; F-216 to K-558; T-217 to K-558; A-218 to K-558; D-219 to K-558; L-220 to K-558; F-221 to K-558; L-222 to K-558; T-223 to K-558; T-224 to K-558; L-225 to K-558; N-226 to K-558; A-227 to K-558; T-228 to K-558; T-229 to K-558; S-230 to K-558; T-231 to K-558; F-232 to K-558; Q-233 to K-558; F-234 to K-558; E-235 to K-558; I-236 to K-558; W-237 to K-558; E-238 to K-558; N-239 to K-558; L-240 to K-558; D-241 to K-558; G-242 to K-558; N-243 to K-558; F-244 to K-558; S-245 to K-558; V-246 to K-558; S-247 to K-558; T-248 to K-558; I-249 to K-558; L-250 to K-558; E-251 to K-558; K-252 to K-558; P-253 to K-558; Q-254 to K-558; N-255 to K-558; M-256 to K-558; M-257 to K-558; V-258 to K-558; V-259 to K-558; G-260 to K-558; Q-261 to K-558; S-262 to K-558; A-263 to K-558; F-264 to K-558; A-265 to K-558; D-266 to K-558; F-267 to K-558; D-268 to K-558; G-269 to K-558; D-270 to K-558; G-271 to K-558; H-272 to K-558; M-273 to K-558; D-274 to K-558; H-275 to K-558; L-276 to K-558; L-277 to K-558; P-278 to K-558; G-279 to K-558; C-280 to K-558; E-281 to K-558; D-282 to K-558; K-283 to K-558; N-284 to K-558; C-285 to K-558; Q-286 to K-558; K-287 to K-558; S-288 to K-558; T-289 to K-558; I-290 to K-558; Y-291 to K-558; L-292 to K-558; V-293 to K-558; R-294 to K-558; S-295 to K-558; G-296 to K-558; M-297 to K-558; K-298 to K-558; Q-299 to K-558; W-300 to K-558; V-301 to K-558; P-302 to K-558; V-303 to K-558; L-304 to K-558; Q-305 to K-558; D-306 to K-558; F-307 to K-558;

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M-1 to Y-479; M-1 to G-478; M-1 to N-477; M-1 to A-476; M-1 to D-475; M-1 to V-474; M-1 to T-473; M-1 to T-472; M-1 to Y-471; M-1 to M-470; M-1 to I-469; M-1 to Y-468; M-1 to P-467; M-1 to G-466; M-1 to P-465; M-1 to Q-464; M-1 to N-463; M-1 to V-462; M-1 to G-461; M-1 to F-460; M-1 to P-459; M-1 to T-458; M-1 to I-457; M-1 to K-456; M-1 to R-455; M-1 to P-454; M-1 to C-453; M-1 to D-452; M-1 to N-451; M-1 to S-450; M-1 to C-449; M-1 to L-448; M-1 to G-447; M-1 to S-446; M-1 to L-445; M-1 to V-444; M-1 to I-443; M-1 to V-442; M-1 to K-441; M-1 to V-440; M-1 to F-439; M-1 to Y-438; M-1 to A-437; M-1 to D-436; M-1 to A-435; M-1 to E-434; M-1 to F-433; M-1 to N-432; M-1 to N-431; M-1 to K-430; M-1 to L-429; M-1 to T-428; M-1 to H-427; M-1 to I-426; M-1 to A-425; M-1 to F-424; M-1 to D-423; M-1 to N-422; M-1 to K-421; M-1 to T-420; M-1 to Y-419; M-1 to G-418; M-1 to K-417; M-1 to S-416; M-1 to L-415; M-1 to V-414; M-1 to V-413; M-1 to I-412; M-1 to D-411; M-1 to L-410; M-1 to I-409; M-1 to G-408; M-1 to D-407; M-1 to E-406; M-1 to Y-405; M-1 to I-404; M-1 to D-403; M-1 to F-402; M-1 to F-401; M-1 to T-400; M-1 to A-399; M-1 to V-398; M-1 to M-397; M-1 to A-396; M-1 to D-395; M-1 to K-394; M-1 to I-393; M-1 to Q-392; M-1 to N-391; M-1 to L-390; M-1 to D-389; M-1 to T-388; M-1 to L-387; M-1 to E-386; M-1 to W-385; M-1 to Y-384; M-1 to V-383; M-1 to K-382; M-1 to F-381; M-1 to M-380; M-1 to R-379; M-1 to R-378; M-1 to A-377; M-1 to E-376; M-1 to E-375; M-1 to C-374; M-1 to S-373; M-1 to A-372; M-1 to N-371; M-1 to N-370; M-1 to C-369; M-1 to P-368; M-1 to V-367; M-1 to N-366; M-1 to E-365; M-1 to L-364; M-1 to L-363; M-1 to F-362; M-1 to A-361; M-1 to Q-360; M-1 to Q-359; M-1 to N-358; M-1 to S-357; M-1 to G-356; M-1 to S-355; M-1 to T-354; M-1 to N-353; M-1 to K-352; M-1 to L-351; M-1 to I-350; M-1 to V-349; M-1 to L-348; M-1 to A-347; M-1 to D-346; M-1 to P-345; M-1 to Y-344; M-1 to G-343; M-1 to D-342; M-1 to M-341; M-1 to N-340; M-1 to Y-339; M-1 to D-338; M-1 to G-337; M-1 to I-336; M-1 to H-335; M-1 to L-334; M-1 to T-333; M-1 to I-332; M-1 to P-331; M-1 to I-330; M-1 to P-329; M-1 to I-328; M-1 to E-327; M-1 to T-326; M-1 to P-325; M-1 to Q-324; M-1 to Q-323; M-1 to E-322; M-1 to D-321; M-1 to V-320; M-1 to F-319; M-1 to P-318; M-1 to V-317; M-1 to F-316; M-1 to G-315; M-1 to W-314; M-1 to L-313; M-1 to T-312; M-1 to G-311; M-1 to K-310; M-1 to N-309; M-1 to S-308; M-1 to F-307; M-1 to D-306; M-1 to Q-305; M-1 to L-304; M-1 to V-303; M-1 to P-302; M-1 to V-301;

M-1 to W-300; M-1 to Q-299; M-1 to K-298; M-1 to M-297; M-1 to G-296; M-1 to S-295; M-1 to R-294; M-1 to V-293; M-1 to L-292; M-1 to Y-291; M-1 to I-290; M-1 to T-289; M-1 to S-288; M-1 to K-287; M-1 to Q-286; M-1 to C-285; M-1 to N-284; M-1 to K-283; M-1 to D-282; M-1 to E-281; M-1 to C-280; M-1 to G-279; M-1 to P-278; M-1 to L-277; M-1 to L-276; M-1 to H-275; M-1 to D-274; M-1 to M-273; M-1 to H-272; M-1 to G-271; M-1 to D-270; M-1 to G-269; M-1 to D-268; M-1 to F-267; M-1 to D-266; M-1 to A-265; M-1 to F-264; M-1 to A-263; M-1 to S-262; M-1 to Q-261; M-1 to G-260; M-1 to V-259; M-1 to V-258; M-1 to M-257; M-1 to M-256; M-1 to N-255; M-1 to Q-254; M-1 to P-253; M-1 to K-252; M-1 to E-251; M-1 to L-250; M-1 to I-249; M-1 to T-248; M-1 to S-247; M-1 to V-246; M-1 to S-245; M-1 to F-244; M-1 to N-243; M-1 to G-242; M-1 to D-241; M-1 to L-240; M-1 to N-239; M-1 to E-238; M-1 to W-237; M-1 to I-236; M-1 to E-235; M-1 to F-234; M-1 to Q-233; M-1 to F-232; M-1 to T-231; M-1 to S-230; M-1 to T-229; M-1 to T-228; M-1 to A-227; M-1 to N-226; M-1 to L-225; M-1 to T-224; M-1 to T-223; M-1 to L-222; M-1 to F-221; M-1 to L-220; M-1 to D-219; M-1 to A-218; M-1 to T-217; M-1 to F-216; M-1 to D-215; M-1 to E-214; M-1 to T-213; M-1 to L-212; M-1 to D-211; M-1 to I-210; M-1 to F-209; M-1 to A-208; M-1 to H-207; M-1 to S-206; M-1 to H-205; M-1 to P-204; M-1 to I-203; M-1 to R-202; M-1 to M-201; M-1 to K-200; M-1 to S-199; M-1 to T-198; M-1 to T-197; M-1 to T-196; M-1 to L-195; M-1 to A-194; M-1 to P-193; M-1 to H-192; M-1 to W-191; M-1 to S-190; M-1 to L-189; M-1 to N-188; M-1 to G-187; M-1 to G-186; M-1 to L-185; M-1 to L-184; M-1 to I-183; M-1 to Q-182; M-1 to P-181; M-1 to Q-180; M-1 to N-179; M-1 to S-178; M-1 to E-177; M-1 to N-176; M-1 to T-175; M-1 to I-174; M-1 to G-173; M-1 to F-172; M-1 to I-171; M-1 to D-170; M-1 to P-169; M-1 to I-168; M-1 to L-167; M-1 to D-166; M-1 to G-165; M-1 to N-164; M-1 to F-163; M-1 to D-162; M-1 to M-161; M-1 to I-160; M-1 to L-159; M-1 to P-158; M-1 to E-157; M-1 to D-156; M-1 to Q-155; M-1 to F-154; M-1 to T-153; M-1 to R-152; M-1 to N-151; M-1 to L-150; M-1 to I-149; M-1 to T-148; M-1 to M-147; M-1 to N-146; M-1 to N-145; M-1 to P-144; M-1 to D-143; M-1 to L-142; M-1 to T-141; M-1 to Q-140; M-1 to N-139; M-1 to Q-138; M-1 to G-137; M-1 to W-136; M-1 to F-135; M-1 to I-134; M-1 to V-133; M-1 to A-132; M-1 to G-131; M-1 to L-130; M-1 to E-129; M-1 to S-128; M-1 to K-127; M-1 to A-126; M-1 to Y-125; M-1 to N-124; M-1 to K-123; M-1 to P-122; M-1 to

L-121; M-1 to Y-120; M-1 to T-119; M-1 to L-118; M-1 to L-117; M-1 to V-116; M-1 to D-115; M-1 to M-114; M-1 to Q-113; M-1 to S-112; M-1 to D-111; M-1 to G-110; M-1 to D-109; M-1 to Y-108; M-1 to D-107; M-1 to G-106; M-1 to P-105; M-1 to V-104; M-1 to V-103; M-1 to S-102; M-1 to T-101; M-1 to I-100; M-1 to L-99; M-1 to A-98; M-1 to S-97; M-1 to H-96; M-1 to N-95; M-1 to K-94; M-1 to F-93; M-1 to S-92; M-1 to V-91; M-1 to K-90; M-1 to V-89; M-1 to K-88; M-1 to P-87; M-1 to K-86; M-1 to F-85; M-1 to Y-84; M-1 to P-83; M-1 to A-82; M-1 to N-81; M-1 to Q-80; M-1 to D-79; M-1 to A-78; M-1 to L-77; M-1 to F-76; M-1 to V-75; M-1 to I-74; M-1 to L-73; M-1 to D-72; M-1 to N-71; M-1 to R-70; M-1 to E-69; M-1 to R-68; M-1 to L-67; M-1 to V-66; M-1 to F-65; M-1 to L-64; M-1 to D-63; M-1 to T-62; M-1 to Q-61; M-1 to K-60; M-1 to D-59; M-1 to S-58; M-1 to N-57; M-1 to L-56; M-1 to D-55; M-1 to G-54; M-1 to F-53; M-1 to A-52; M-1 to A-51; M-1 to L-50; M-1 to T-49; M-1 to G-48; M-1 to W-47; M-1 to A-46; M-1 to E-45; M-1 to A-44; M-1 to G-43; M-1 to F-42; M-1 to L-41; M-1 to E-40; M-1 to A-39; M-1 to T-38; M-1 to V-37; M-1 to N-36; M-1 to H-35; M-1 to L-34; M-1 to A-33; M-1 to R-32; M-1 to A-31; M-1 to P-30; M-1 to V-29; M-1 to P-28; M-1 to G-27; M-1 to V-26; M-1 to G-25; M-1 to L-24; M-1 to L-23; M-1 to A-22; M-1 to L-21; M-1 to G-20; M-1 to A-19; M-1 to L-18; M-1 to L-17; M-1 to P-16; M-1 to S-15; M-1 to F-14; M-1 to L-13; M-1 to A-12; M-1 to W-11; M-1 to S-10; M-1 to S-9; M-1 to P-8; M-1 to L-7; and M-1 to R-6 of SEQ ID NO:128. Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the

application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209877, where this portion excludes any integer of amino acid residues from 1 to about 606 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209877, or any integer of amino acid residues from 6 to about 612 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209877. Polypeptides encoded by these polynucleotides also are encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Additional preferred polypeptide fragments of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: M-1 to S-15; A-2 to P-16; A-3 to L-17; A-4 to L-18; G-5 to A-19; R-6 to G-20; L-7 to L-21; P-8 to A-22; S-9 to L-23; S-10 to L-24; W-11 to G-25; A-12 to V-26; L-13 to G-27; F-14 to P-28; S-15 to V-29; P-16 to P-30; L-17 to A-31; L-18 to R-32; A-19 to A-33; G-20 to L-34; L-21 to H-35; A-22 to N-36; L-23 to V-37; L-24 to T-38; G-25 to A-39; V-26 to E-40; G-27 to L-41; P-28 to F-42; V-29 to G-43; P-30 to A-44; A-31 to E-45; R-32 to A-46; A-33 to W-47; L-34 to G-48; H-35 to T-49; N-36 to L-50; V-37 to A-51; T-38 to A-52; A-39 to F-53; E-40 to G-54; L-41 to D-55; F-42 to L-56; G-43 to N-57; A-44 to S-58; E-45 to D-59; A-46 to K-60; W-47 to Q-61; G-48 to T-62; T-49 to D-63; L-50 to L-64; A-51 to F-65; A-52 to V-66; F-53 to L-67; G-54 to R-68; D-55 to

E-69; L-56 to R-70; N-57 to N-71; S-58 to D-72; D-59 to L-73; K-60 to I-74; Q-61 to V-75; T-62 to F-76; D-63 to L-77; L-64 to A-78; F-65 to D-79; V-66 to Q-80; L-67 to N-81; R-68 to A-82; E-69 to P-83; R-70 to Y-84; N-71 to F-85; D-72 to K-86; L-73 to P-87; I-74 to K-88; V-75 to V-89; F-76 to K-90; L-77 to V-91; A-78 to S-92; D-79 to F-93; Q-80 to K-94; N-81 to N-95; A-82 to H-96; P-83 to S-97; Y-84 to A-98; F-85 to L-99; K-86 to I-100; P-87 to T-101; K-88 to S-102; V-89 to V-103; K-90 to V-104; V-91 to P-105; S-92 to G-106; F-93 to D-107; K-94 to Y-108; N-95 to D-109; H-96 to G-110; S-97 to D-111; A-98 to S-112; L-99 to Q-113; I-100 to M-114; T-101 to D-115; S-102 to V-116; V-103 to L-117; V-104 to L-118; P-105 to T-119; G-106 to Y-120; D-107 to L-121; Y-108 to P-122; D-109 to K-123; G-110 to N-124; D-111 to Y-125; S-112 to A-126; Q-113 to K-127; M-114 to S-128; D-115 to E-129; V-116 to L-130; L-117 to G-131; L-118 to A-132; T-119 to V-133; Y-120 to I-134; L-121 to F-135; P-122 to W-136; K-123 to G-137; N-124 to Q-138; Y-125 to N-139; A-126 to Q-140; K-127 to T-141; S-128 to L-142; E-129 to D-143; L-130 to P-144; G-131 to N-145; A-132 to N-146; V-133 to M-147; I-134 to T-148; F-135 to I-149; W-136 to L-150; G-137 to N-151; Q-138 to R-152; N-139 to T-153; Q-140 to F-154; T-141 to Q-155; L-142 to D-156; D-143 to E-157; P-144 to P-158; N-145 to L-159; N-146 to I-160; M-147 to M-161; T-148 to D-162; I-149 to F-163; L-150 to N-164; N-151 to G-165; R-152 to D-166; T-153 to L-167; F-154 to I-168; Q-155 to P-169; D-156 to D-170; E-157 to I-171; P-158 to F-172; L-159 to G-173; I-160 to I-174; M-161 to T-175; D-162 to N-176; F-163 to E-177; N-164 to S-178; G-165 to N-179; D-166 to Q-180; L-167 to P-181; I-168 to Q-182; P-169 to I-183; D-170 to L-184; I-171 to L-185; F-172 to G-186; G-173 to G-187; I-174 to N-188; T-175 to L-189; N-176 to S-190; E-177 to W-191; S-178 to H-192; N-179 to P-193; Q-180 to A-194; P-181 to L-195; Q-182 to T-196; I-183 to T-197; L-184 to T-198; L-185 to S-199; G-186 to K-200; G-187 to M-201; N-188 to R-202; L-189 to I-203; S-190 to P-204; W-191 to H-205; H-192 to S-206; P-193 to H-207; A-194 to A-208; L-195 to F-209; T-196 to I-210; T-197 to D-211; T-198 to L-212; S-199 to T-213; K-200 to E-214; M-201 to D-215; R-202 to F-216; I-203 to T-217; P-204 to A-218; H-205 to D-219; S-206 to L-220; H-207 to F-221; A-208 to L-222; F-209 to T-223; I-210 to T-224; D-211 to L-225; L-212 to N-226; T-213 to A-227; E-214 to T-228; D-215 to T-229; F-216 to S-230; T-217 to T-231; A-218 to F-232; D-219 to Q-233; L-220 to F-234; F-221 to E-235; L-

222 to I-236; T-223 to W-237; T-224 to E-238; L-225 to N-239; N-226 to L-240; A-227 to D-241; T-228 to G-242; T-229 to N-243; S-230 to F-244; T-231 to S-245; F-232 to V-246; Q-233 to S-247; F-234 to T-248; E-235 to I-249; I-236 to L-250; W-237 to E-251; E-238 to K-252; N-239 to P-253; L-240 to Q-254; D-241 to N-255; G-242 to M-256; N-243 to M-257; F-244 to V-258; S-245 to V-259; V-246 to G-260; S-247 to Q-261; T-248 to S-262; I-249 to A-263; L-250 to F-264; E-251 to A-265; K-252 to D-266; P-253 to F-267; Q-254 to D-268; N-255 to G-269; M-256 to D-270; M-257 to G-271; V-258 to H-272; V-259 to M-273; G-260 to D-274; Q-261 to H-275; S-262 to L-276; A-263 to L-277; F-264 to P-278; A-265 to G-279; D-266 to C-280; F-267 to E-281; D-268 to D-282; G-269 to K-283; D-270 to N-284; G-271 to C-285; H-272 to Q-286; M-273 to K-287; D-274 to S-288; H-275 to T-289; L-276 to I-290; L-277 to Y-291; P-278 to L-292; G-279 to V-293; C-280 to R-294; E-281 to S-295; D-282 to G-296; K-283 to M-297; N-284 to K-298; C-285 to Q-299; Q-286 to W-300; K-287 to V-301; S-288 to P-302; T-289 to V-303; I-290 to L-304; Y-291 to Q-305; L-292 to D-306; V-293 to F-307; R-294 to S-308; S-295 to N-309; G-296 to K-310; M-297 to G-311; K-298 to T-312; Q-299 to L-313; W-300 to W-314; V-301 to G-315; P-302 to F-316; V-303 to V-317; L-304 to P-318; Q-305 to F-319; D-306 to V-320; F-307 to D-321; S-308 to E-322; N-309 to Q-323; K-310 to Q-324; G-311 to P-325; T-312 to T-326; L-313 to E-327; W-314 to I-328; G-315 to P-329; F-316 to I-330; V-317 to P-331; P-318 to I-332; F-319 to T-333; V-320 to L-334; D-321 to H-335; E-322 to I-336; Q-323 to G-337; Q-324 to D-338; P-325 to Y-339; T-326 to N-340; E-327 to M-341; I-328 to D-342; P-329 to G-343; I-330 to Y-344; P-331 to P-345; I-332 to D-346; T-333 to A-347; L-334 to L-348; H-335 to V-349; I-336 to I-350; G-337 to L-351; D-338 to K-352; Y-339 to N-353; N-340 to T-354; M-341 to S-355; D-342 to G-356; G-343 to S-357; Y-344 to N-358; P-345 to Q-359; D-346 to Q-360; A-347 to A-361; L-348 to F-362; V-349 to L-363; I-350 to L-364; L-351 to E-365; K-352 to N-366; N-353 to V-367; T-354 to P-368; S-355 to C-369; G-356 to N-370; S-357 to N-371; N-358 to A-372; Q-359 to S-373; Q-360 to C-374; A-361 to E-375; F-362 to E-376; L-363 to A-377; L-364 to R-378; E-365 to R-379; N-366 to M-380; V-367 to F-381; P-368 to K-382; C-369 to V-383; N-370 to Y-384; N-371 to W-385; A-372 to E-386; S-373 to L-387; C-374 to T-388; E-375 to D-389; E-376 to L-390; A-377 to N-391; R-378 to Q-392; R-379 to I-393; M-380 to K-394; F-381 to D-

395; K-382 to A-396; V-383 to M-397; Y-384 to V-398; W-385 to A-399; E-386 to T-400; L-387 to F-401; T-388 to F-402; D-389 to D-403; L-390 to I-404; N-391 to Y-405; Q-392 to E-406; I-393 to D-407; K-394 to G-408; D-395 to I-409; A-396 to L-410; M-397 to D-411; V-398 to I-412; A-399 to V-413; T-400 to V-414; F-401 to L-415; F-402 to S-416; D-403 to K-417; I-404 to G-418; Y-405 to Y-419; E-406 to T-420; D-407 to K-421; G-408 to N-422; I-409 to D-423; L-410 to F-424; D-411 to A-425; I-412 to I-426; V-413 to H-427; V-414 to T-428; L-415 to L-429; S-416 to K-430; K-417 to N-431; G-418 to N-432; Y-419 to F-433; T-420 to E-434; K-421 to A-435; N-422 to D-436; D-423 to A-437; F-424 to Y-438; A-425 to F-439; I-426 to V-440; H-427 to K-441; T-428 to V-442; L-429 to I-443; K-430 to V-444; N-431 to L-445; N-432 to S-446; F-433 to G-447; E-434 to L-448; A-435 to C-449; D-436 to S-450; A-437 to N-451; Y-438 to D-452; F-439 to C-453; V-440 to P-454; K-441 to R-455; V-442 to K-456; I-443 to I-457; V-444 to T-458; L-445 to P-459; S-446 to F-460; G-447 to G-461; L-448 to V-462; C-449 to N-463; S-450 to Q-464; N-451 to P-465; D-452 to G-466; C-453 to P-467; P-454 to Y-468; R-455 to I-469; K-456 to M-470; I-457 to Y-471; T-458 to T-472; P-459 to T-473; F-460 to V-474; G-461 to D-475; V-462 to A-476; N-463 to N-477; Q-464 to G-478; P-465 to Y-479; G-466 to L-480; P-467 to K-481; Y-468 to N-482; I-469 to G-483; M-470 to S-484; Y-471 to A-485; T-472 to G-486; T-473 to Q-487; V-474 to L-488; D-475 to S-489; A-476 to Q-490; N-477 to S-491; G-478 to A-492; Y-479 to H-493; L-480 to L-494; K-481 to A-495; N-482 to L-496; G-483 to Q-497; S-484 to L-498; A-485 to P-499; G-486 to Y-500; Q-487 to N-501; L-488 to V-502; S-489 to L-503; Q-490 to G-504; S-491 to L-505; A-492 to G-506; H-493 to R-507; L-494 to S-508; A-495 to A-509; L-496 to N-510; Q-497 to F-511; L-498 to L-512; P-499 to D-513; Y-500 to H-514; N-501 to L-515; V-502 to Y-516; L-503 to V-517; G-504 to G-518; L-505 to I-519; G-506 to P-520; R-507 to R-521; S-508 to P-522; A-509 to S-523; N-510 to G-524; F-511 to E-525; L-512 to K-526; D-513 to S-527; H-514 to I-528; L-515 to R-529; Y-516 to K-530; V-517 to Q-531; G-518 to E-532; I-519 to W-533; P-520 to T-534; R-521 to A-535; P-522 to I-536; S-523 to I-537; G-524 to P-538; E-525 to N-539; K-526 to S-540; S-527 to Q-541; I-528 to L-542; R-529 to I-543; K-530 to V-544; Q-531 to I-545; E-532 to P-546; W-533 to Y-547; T-534 to P-548; A-535 to H-549; I-536 to N-550; I-537 to V-551; P-538 to P-552; N-539 to R-553; S-540 to S-554; Q-541 to W-

555; L-542 to S-556; I-543 to A-557; V-544 to K-558; I-545 to L-559; P-546 to Y-560; Y-547 to L-561; P-548 to T-562; H-549 to P-563; N-550 to S-564; V-551 to N-565; P-552 to I-566; R-553 to V-567; S-554 to L-568; W-555 to L-569; S-556 to T-570; A-557 to A-571; K-558 to I-572; L-559 to A-573; Y-560 to L-574; L-561 to I-575; T-562 to G-576; P-563 to V-577; S-564 to C-578; N-565 to V-579; I-566 to F-580; V-567 to I-581; L-568 to L-582; L-569 to A-583; T-570 to I-584; A-571 to I-585; I-572 to G-586; A-573 to I-587; L-574 to L-588; I-575 to H-589; G-576 to W-590; V-577 to Q-591; C-578 to E-592; V-579 to K-593; F-580 to K-594; I-581 to A-595; L-582 to D-596; A-583 to D-597; I-584 to R-598; I-585 to E-599; G-586 to K-600; I-587 to R-601; L-588 to Q-602; H-589 to E-603; W-590 to A-604; Q-591 to H-605; E-592 to R-606; K-593 to F-607; K-594 to H-608; A-595 to F-609; D-596 to D-610; D-597 to A-611; and R-598 to M-612 of SEQ ID NO:128. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain disorders and diseases of developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and fetal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural,

developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

Interferons (IFNs) are a well known family of cytokines secreted by a large variety of eukaryotic cells upon exposure to various mitogens. The interferons have been classified by their chemical and biological characteristics into three groups: IFN-alpha (leukocytes), IFN-beta (fibroblasts), and IFN-gamma (lymphocytes). IFN-alpha and beta are known as Type I interferons; IFN-gamma is known as Type II or immune interferon. The IFNs exhibit anti-viral, immunoregulatory, and antiproliferative activity. The clinical potential of interferons is widely recognized.

IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory

proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.

Polypeptides of the invention were found to induce secretion of IFNγ when added to PBLs in the presence of anti-CD3 and anti-CD28 (See assay, Example 33). Therefore, it is likely that polynucleotides or polypeptides of the invention and/or agonists and/or antagonists thereof would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes suggests a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as

autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Polynucleotides or polypeptides of the invention and/or agonists and/or antagonists thereof, are used to treat, prevent, and/or diagnose diseases and disorders of the pulmonary system (e.g., bronchi such as, for example, sinopulmonary and bronchial infections) and conditions associated with such diseases and disorders and other respiratory diseases and disorders. In specific embodiments, such diseases and disorders include, but are not limited to, pulmonary fibrosis, bronchial adenoma, bronchial asthma, pneumonia (such as, e.g., bronchial pneumonia, bronchopneumonia, and tuberculous bronchopneumonia), chronic obstructive pulmonary disease (COPD), bronchial polyps, bronchiectasia (such as, e.g., bronchiectasia sicca, cylindrical bronchiectasis, and saccular bronchiectasis), bronchiolar adenocarcinoma, bronchiolar carcinoma, bronchiolitis (such as, e.g., exudative bronchiolitis, bronchiolitis fibrosa obliterans, and proliferative bronchiolitis), bronchiolo-alveolar carcinoma, bronchitic asthma, bronchitis (such as, e.g., asthmatic bronchitis, Castellani's bronchitis, chronic bronchitis, croupous bronchitis, fibrinous bronchitis, hemorrhagic bronchitis, infectious avian bronchitis, obliterative bronchitis, plastic bronchitis, pseudomembranous bronchitis, putrid bronchitis, and verminous bronchitis), bronchocentric granulomatosis, bronchoedema, bronchoesophageal fistula, bronchogenic carcinoma, bronchogenic cyst, broncholithiasis, bronchomalacia, bronchomycosis (such as, e.g., bronchopulmonary aspergillosis), bronchopulmonary spirochetosis, hemorrhagic bronchitis, bronchorrhea, bronchospasm, bronchostaxis, bronchostenosis, Biot's respiration, bronchial respiration, Kussmaul respiration, Kussmaul-Kien respiration, respiratory acidosis, respiratory alkalosis, respiratory distress syndrome of the newborn, respiratory insufficiency, respiratory scleroma, respiratory syncytial virus, and the like.

In addition, expression of this gene in lung and the ability of polypeptides of the invention to induce interferon gamma production indicates that the polynucleotides and/or polypeptides corresponding to this gene, (and/or antibodies raised against those polypeptides) are particularly useful in the diagnosis and treatment of diseases and disorder of the lung or lung function including for example, lung cancer, pulmonary edema, pulmonary fibrosis, respiratory distress syndrome, asthma, bronchitis, and infections that affect the lung such as influenza and pneumonia. It is specifically contemplated that the polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof could be delivered to the patient as a therapeutic into the lungs by way of inhalants, spray mist, or other delivery systems that involve directly inhaling the therapeutic.

The fact that polypeptides of the invention have been found to induce secretion of IFNγ when added to PBLs indicates that polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof would be useful for the treatment and/or diagnosis of a variety of diseases and disorders. Examples of viral diseases and disorders that can be treated or prevented using polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof, include, but are not limited to, the following: AIDS, viral hepatitis including chronic hepatitis B and hepatitis C, papilloma viruses, herpes, cytomegalovirus (CMV), viral encephalitis, and in the prophylaxis of rhinitis.

Examples of antiparasitic and bacterial diseases and disorders using polynucleotides and polypeptides of the invention, or fragments, variants, antagonists/agonists and derivatives thereof, include, but are not limited to, the following: Cryptosporidium parvum infection and multidrug-resistant pulmonary tuberculosis.

Polynucleotides or polypeptides of the invention and/or agonists and/or antagonists thereof, may be useful as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting

of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

Polynucleotides or polypeptides of the invention and/or agonists and/or antagonists thereof, may be useful as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli,* Enterohemorrhagic *E. coli, Borrelia burgdorferi*, and Plasmodium (malaria).

Polynucleotides or polypeptides of the invention and/or agonists and/or antagonists thereof, may be useful as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

Examples of cancers that can be treated or prevented using polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof,

include, but are not limited to, the following: hairy cell leukemia, acute myeloid leukemia, osteosarcoma, basal cell carcinoma, glioma, renal cell carcinoma, multiple myeloma, melanoma, Hodgkin's disease, synergistic treatment of advanced cancer with a combination of alpha interferon and temozolomide. Representative uses are described in the "Hyperproliferative Disorders" and "Immune Activity" sections below and elsewhere herein.

Polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof may also be useful in immunotherapies. For example, immunosuppression such as the prevention of graft vs. host rejection or to curtail the progression of autoimmune diseases, such as arthritis, multiple sclerosis, and/or diabetes.

In addition, polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof may also be useful for anti-allergy treatments or vaccine adjuvantation.

Alternatively, polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof may be employed clinically to stimulate interferon production in a mammalian, preferably human, host. Particularly, the polypeptides of the present invention, including fragments, variants, and derivatives thereof, may be administered to a patient (e.g., mammal, preferably human), to stimulate alpha, beta, and/or gamma interferon production. Thus, polypeptides, fragments, variants, and derivatives of the present invention have prophylactic and therapeutic uses which include, but are not limited to, anti-viral therapy, anti-cancer therapy, anti-parasitic therapy, anti-bacterial therapy, treatment and prevention of allergy, immunotherapy, and/or in the treatment of any condition, such as those mentioned above, where an increased production of interferon is desired. The polypeptides of the invention may also be used as an adjuvant or co-adjuvant to enhance or stimulate the immune response in cases of prophylactic or therapeutic vaccination.

Further, there is provided a method of treating infection in a patient comprising administering an effective amount of a polypeptide, or fragment, variant, or derivative of the invention to a patient in need of anti-infective

therapy. In a preferred embodiment the infection is of viral, bacterial, or parasitic etiology. In a particularly preferred embodiment, the infection is a viral infection.

Further, there is provided a method of treating cancer in a patient comprising administering an effective amount of a polypeptide, or fragment, variant, or derivative of the invention to a patient in need of anti-cancer therapy.

Polynucleotides of the invention may also be employed in gene therapy to treat patients in need of increased interferon production. Representative uses are described in the "Gene Therapy" section below. Such patients include those in need of anti-viral, anti-bacterial, anti-parasitic, anti-cancer therapy, or immunotherapy.

The tissue distribution in neural tissues and developing tissues indicates that polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof are useful for the treatment and/or diagnosis of disorders of the central nervous system, disorders of developing systems, and cancers.

The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, multiple sclerosis, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

The tissue distribution in placenta indicates that polynucleotides and polypeptides of the invention, or fragments, variants, and derivatives thereof are useful for the diagnosis and/or treatment of disorders of the placenta. Relatively high expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta

also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg.

Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis.

Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.

Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: MTKREDGGYTFTATPEDFPKKHKAPVIDIGIANTGKFIMTASSDTTVLIWSLK GQVLSTINTNQMNNTHAAVSPCGRFVASCGFTPDVKVWEVCFGKKGEFQEV VRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWKLWDTXVEYKKKQDPY LLKTGRFEEAAGAXPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGHLKRASNEST RQRLQQQLTQAQETLKSLGALKK (SEQ ID NO: 231). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes

which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 12 - 28 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: VIRHEGSTNMELSQMSXLMGLSVLLGLLALMATAAVXRGWLRAGEERSGRP ACQKANGFPPDKSSGSKKQKQYQRIRKEKPQQHNFTHRLLAAALKSHSGNIS CMDFSSNGKYLATCADDRTIRIWSTKDFLQREHRSMRANVELDHATLVRFSP DCRAFIVWLANGDTLRVFKMTKREDGGYTFTATPEDFPKKHKAPVIDIGIAN TGKFIMTASSDTTVLIWSLKGQVLSTINTNQMNNTHAAVSPCGRFVASCGFTP DVKVWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGT WKLWDTXVEYKKKQDPYLLKTGRFEEAAGAXPCRLALSPNAQVLALASGSS IHLYNTRRGEKEECFERVHGECIANLSFDITGRFLASCGDRAVRLFHNTPGHR AMVEEMQGHLKRASNESTRQRLQQQLTQAQETLKSLGALKK (SEQ ID NO: 232). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in testes, synovial sarcoma and fetal tissues, and to a lesser extent in several other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the reproductive and developing systems and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, seminal fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes tissue, synovial sarcoma, and fetal tissues, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of the reproductive and developing systems, and cancers.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target

indications. Furthermore, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders.

Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division.

Additionally, the expression in hematopoietic cells and tissues indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. This protein is useful for the treatment, detection, and/or prevention of William's disease. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group: 1-363, 2-363, 4-363, 5-363, 30-363, 31-363, 32-363, 75-363, 76-363 and 82-363 of the following amino acid sequence:

MSVMVVRKKVTRKWEKLPGRNTFCCDGRVMMARQKGIFYLTLFLILGTCTL
FFAFECRYLAVQLSPAIPVFAAMLFLFSMATLLRTSFSDPGVIPRALPDEAAFIE
MEIEATNGAVPQGQRPPPRIKNFQINNQIVKLKYCYTCKIFRPPRASHCSICDN
CVERFDHHCPWVGNCVGKRNYRYFYLFILSLSLLTIYVFAFNIVYVALKSLKI
GFLETLKETPGTVLEVLICFFTLWSVVGLTGFHTFLVALNQTTNEDIKGSWTG

KNRVQNPYSHGNIVKNCCEVLCGPLPPSVLDRRGILPLEESGSRPPSTQETSSS LLPQSPAPTELNSNEMPEDSSTPEEMPPPEPPEPPQEAAEAEK (SEQ ID NO: 233). Polynucleotides encoding such polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

A preferred polypeptide variant of the invention comprises the following amino acid sequence:

MLFLFSMATLLRTSFSDPGVIPRALPDEAAFIEMEIEATNGAVPQGQRPPPRIK NFQINN QIVKLKYCYTCKIFRPPRASHCSICDNCVE RFDHHCPWVGNCVGKRNYRYFYLFILSLSL LTIYVFAFNIVYVALKSLKIGFLETLKGNS WNCSRSPHLLLYTLVRRGTDWISYFPRGSQ PDNQ (SEQ ID NO: 234). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in ovarian and endometrial tumors, fetal liver, spleen and brain tissues, and to a lesser extent in several other tissues and organs.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the developing systems, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing, female reproductive and fetal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 130 as residues: Pro-44 to Lys-54, Cys-88 to His-95, Val-103 to Tyr-108, Gln-181 to Ser-190, Thr-192 to Ile-206, Glu-233 to Ser-245, Ser-252 to Ala-286. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in developing systems indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of disorders of developing and fetal systems, and cancers. Furthermore, the tissue distribution in ovarian and endometrial tumor tissues indicates that the translation product of this clone is useful for the detection, diagnosis, and/or treatment of cancers of the female reproductive system. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting these tumors. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other

treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in normal and cancerous colon tissue, macrophages, endothelial cells and placental tissue, and to a lesser extent in several other tissues and organs.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, colon cancer and gastrointestinal disorders, immune disorders, vascular diseases and disorders of developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune , vascular and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, gastrointestinal, developmental, vascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 131 as residues: Thr-27 to Ser-33. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in macrophage, endothelial and placental tissues, and normal and cancerous colon tissues, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of immune, gastrointestinal and vascular disorders and diseases. Expression of this gene product

in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting colon cancer. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting colon cancer in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

Alternatively, the tissue distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta and endothelial cells also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body.

Additionally, expression of this gene product in macrophage also strongly indicates a role for this protein in immune function and immune surveillance. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of

cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The translation product of this gene shares homology with HNK-sulfotransferase, which directs glycan synthesis (see, e.g., Genbank Accession no. AF033827).

This gene is expressed primarily in activated T cells, osteoclastoma, and glioblastoma, and to a lesser extent in various other normal and transformed cell types.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, immune defects, cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hemopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative

to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 132 as residues: Pro-32 to Gly-48, Gln-63 to Thr-69, Pro-77 to Trp-84, Val-88 to Leu-94. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in T-cells and various types of neoplasms indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, study and/or treatment of inflammatory and general immune defects, and various types of neoplasms. Expression of this gene product in T cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the tissue distribution in various cancerous tissues indicates that the translation product of the clone is useful for the detection, diagnosis, and/or treatment of these cancers, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

Preferred polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
LHECLPGSISYLHPRTPWLCLPPQHLSFSTFSPPWQPAMSPVPGTGGPPCGL (SEQ ID NO: 235), and/or
MLPLLIICLLPAIEGKNCLRCWPELSALIDYDLQILWVTPGPPTELSQSIHSLFLE DNNFLK
PWYLDRDHLEEETAKFFTQVHQAIKTLRDDKTVLLEEIYTHKNLFTERLNKIS DGLKEKGAPPLHECLP
GSISYLHPRTPWLCLPPQHLSFSTFSPPWQPAMSPVPGTGGPPCGL (SEQ ID NO: 236). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in infant brain, testes and activated T cells, and to a lesser extent in various other normal and transformed cell types.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, reproductive and inflammatory conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural, immune and male reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken

from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 133 as residues: Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Ala-123. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in infant brain tissue, testes tissue, and activated T-cells, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study, diagnosis, and/or treatment of neurological, reproductive and immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell type.

Alternatively, the tissue distribution in testes tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful

in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Furthermore, the tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The translation product of this gene shares sequence homology with some human and rodent melanoma and leukocyte specific antigens (see, for example, Genbank accession nos: gi|189384, gi|205898 and gi|180926). In addition, the translation product of this gene shares sequence homology with Tetraspan protein (see, for example, Genbank accession number: GI 3152703). Therefore, it is likely that the polypeptide of this gene shares some biological functions, such as cell-to-cell signaling, adhesion, proliferation, and differentiation with Tetraspan.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 52-68 and 197 - 213 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

The transmembrane 4 superfamily (TM4SF) or tetraspan superfamily has at least 16 members (including CD9, CD20, CD37, CD53, CD63, CD81, CD82, A15, CO-029, Sm23, RDS, Uro B, Uro A, SAS, Rom-1, PETA3, and YKK8), is the second biggest subfamily among CD antigen superfamily. and activation antigen of T- cells. All TM4SF member contains four putative transmembrane domains, two extracellular loops, and two short cytoplasmic tails. They are variously expressed on Immature, early, mature, activated lymphocytes, monocytes, macrophages, granulocytes, platelets, eosinophils, basophils, certain leukemic and lymphoma cells, and a variety of other cells and tissues. CD9 cell surface protein is expressed by both hematopoietic and neural cells, and may play a role for CD9 in intercellular signaling in the immune and nervous system. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule, which play important role in cell adhesion of platelets and endothelial cells. Increased mRNA for CD63 antigen was found in atherosclerotic lesions of Watanabe heritable hyperlipidemic rabbits, suggesting a potential role of CD63 in progression of atherosclerosis. CD63 is also a mast cell marker. CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be a target for the development of a drug for this leukemia. CD81 is the target of an antiproliferative antibody. A diverse group of human cell lines, including hematolymphoid, neuroectodermal, and mesenchymal cells, express the CD81 protein. Many of the lymphoid cell lines, in particular those derived from large cell lymphomas, were susceptible to the antiproliferative effects of the antibody. CD81 may therefore play an important role in the regulation of lymphoma cell growth. CD9, CD20, CD37, CD63, CD81 and CD82 have been implicated in the regulation of cell growth, adhesion, and signal transduction of B, T lymphocytes and some other non-lymphoid cells. They associate with CD2, CD21, CD4, CD8, MHC Class II molecules, integrins, function as co-receptor for T, B and other lymphoid cells. Some TM4SF are leukocyte antigens, highly expressed in activated leukocytes, lymphocytes, are highly specific surface marker for lymphoblastic leukemia, lymphoma, melanoma, and neuroblastoma. CD9 has been show to be involved in cell motility and tumor metastasis. These antigens could be a valuable immunogen or

target to implement active and passive immunotherapy in patients with cancer. Others have been shown to be involved in inhibition of prostate cancer metastasis. This gene has close homology to C33 antigen (CD82). whic is a member of the transmembrane 4 superfamily (TMSF) and activation antigen of T- cells. C33 Ag (CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be very important target for developing drug for leukemia. Other members of this family are Sm23, CO-029, R2, TAPA-1, CD9, CD37, CD53, and CD63. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule. There are strong evidence indicating that CD63 and Pltgp40, a platelet membrane glycoprotein are the same molecule and that CD63/Pltgp40 is identical to the well-characterized, stage-specific melanoma-associated antigen ME491. These antigen could be valuable immunogens or target to implement active and passive immunotherapy in patients with cancer.

This gene is expressed primarily in fetal tissue (kidney, heart, liver, spleen, brain), macrophages, dendritic cells, retina and to a lesser extent in various other tissues, mostly of lymphoid origin or epithelial cell types. In addition This gene is expressed in cancerous tissues (e.g. breast).

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders and cancers in a variety of organs and cell types. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, proliferating, immune, hematopoietic, integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid, spinal fluid, or amniotic fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression

level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 134 as residues: Tyr-123 to Tyr-131, Cys-134 to Ser-145, Tyr-234 to Tyr-244. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution fetal cells and tissues and homology to tumor antigens indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of lymphoid and epithelial disorders and neoplasms.

Additionally, tissue distribution in immune cells and other tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoesis, including cancers. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that

influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene shares limited sequence homology with VEGF which is thought to be important in regulation of endothelial cell growth. Therefore, it is likely that the protein encoded by this gene would share some similar biological functions. When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed in brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, nervous system disease and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 135 as

residues: Thr-25 to Pro-46. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in brain indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The translation product of this gene shares sequence homology with human p150 which is thought to be important in signal transduction in neuronal cells. Therefore, it is likely that the protein encoded by this polynucleotide would share some similar biological functions with p150.

This gene is expressed primarily in whole embryo and cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and growth defects/disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for study and treatment of central nervous system, neurodevelopmental, cognitive, and memory disorders.

The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function.

Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene is expressed primarily in PMA stimulated HL-60 cells and to a lesser extent in 6 week embryo.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting cell differentiation, particularly hematopoietic disorders and/or defects. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 137 as residues: Pro-61 to Asp-68. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the study of cellular differentiation and for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. The tissue distribution also indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or

other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and/or defects of the digestive tract including but not limited to cancers of the gastrointestinal tract. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the digestive system particularly disorders involving the colon. Further, expression of this gene product in colon tissue indicates involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the colon and/or other gastrointestinal tissue including, but not limited to, stomach, small intestine, large intestine, and rectum.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

This gene is expressed primarily in blood cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 139 as residues: Pro-19 to Cys-29, Thr-35 to Glu-44, Val-72 to Lys-78. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis and/or treatment of disorders of the immune and hematopoietic system. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

FEATURES OF PROTEIN ENCODED BY GENE NO: 37

This gene is expressed in multiple tissue systems such as brain, immune cells, prostate, uterus, testes, placenta, and fetal heart as well as in cancerous tissues such as ovarian tumors. .

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune, reproductive, urogenital, and central nervous system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous sytem and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, urogenital, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 140 as residues: Tyr-33 to Lys-38. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, urogenital, reproductive, and central nervous systems. The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors.

The tissue distribution in central nervous system tissues also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo. .

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution in uterus indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally.

Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium.

The tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene is expressed in a wide range of tissue systems such as brain, immune cells, fetal liver, kidney, testes, breast, and pancreas as well as cancerous tissue such as ovarian tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the central nervous system, immune system, urogenital, and reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, CNS, urogenital, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 141 as residues: Met-1 to Ser-7, Asp-32 to Pro-43, Ser-96 to Arg-102. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, reproductive, urogenital and central nervous systems.

The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of diseases of the central nervous system, as well as cancers of tissues where expression of this gene has been observed, such as in ovarian tumors.

The tissue distribution in central nervous system tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention

of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

This gene is expressed primarily in macrophages and fetal cells and to a lesser extent in cancerous ovarian tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases, disorders of developing tissues, and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of developmental abnormalities and disorders of the immune systems.

The tissue distribution cancerous ovaries indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Expression of this gene product in macrophage cells strongly indicates a role for this protein in immune function and immune surveillance. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation.

The tissue distribution indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the

expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may

also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The tissue distribution also indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders such as melanomas.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

This gene is expressed primarily in neutrophils, bone marrow, brain, and fetal cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders, Limbic system dysfunction/defects and disorders of the immune system and developing systems. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, Limbic system and developing systems, expression of this gene at significantly higher or lower levels may be

routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 143 as residues: Ala-84 to Gln-93. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of disorders of the immune, Limbic system, CNS and developing systems. Expression of this gene product in bone marrow, eosinophils, and neutrophils strongly indicates a role for this protein in hematopoiesis and immune surveillance. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). This gene product may have clinical utility in the treatment of immune dysfunction; in the correction of autoimmunity; in immune modulation; and in the control of inflammation.

The tissue distribution indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis,

granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be

used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 41

When tested against MVEC endothelial cell lines, supernatants removed from cells containing this gene activated the expression of ICAM-1. Thus, this gene activates signal transduction pathways which upregulate cell-surface expression and/or secretion of ICAM-1. ICAM-1 - is found on the cell surface of endothelial cells, smooth muscle cells, epithelial cells, and fibroblasts. It binds to its ligand, LFA-1, a heterodimer complex that is a member of the leukocyte integrin family of cell adhesion receptors. Inflammatory mediators and cytokines, such as, IL-1, TNFa and IFNg, stimulate ICAM-1 expression on vascular cells, in addition to the aforementioned cells and tissue cell types. Polypeptides which increase ICAM expression are useful in the treatment of cancer, cardiovascular, autoimmune and inflammatory diseases and/or disorders.

This gene is expressed primarily in ovary and to a lesser extent in fetal tissue, colon, and immune cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, gastrointestinal and immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, gastrointestinal, immune,

cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 144 as residues: Ile-23 to Ala-29. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of ovarian cancer and related metastases. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility.

The tissue distribution in colon tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the gastrointestinal tract. This may include diseases associated with digestion and food absorption, as well as hematopoietic disorders involving the Peyer's patches of the small intestine, or other hematopoietic cells and tissues within the body. Similarly, expression of this gene product in colon tissue indicates again involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene shares sequence homology with retrovirus-related reverse transcriptase pseudogene. In addition, this gene shares homology with human interferon-beta (Genseq accession number T35524; all references available through this accession are hereby incorporated herein by reference), therefore, it is likely that this gene and the protein encoded by this gene shares some similar biological functions with this protein.

This gene is expressed primarily in frontal cortex.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in frontal cortex and homology to retrovirus-related reverse transcriptase pseudogene and human interferon-beta indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative diseases of the brain, particularly of the frontal cortex. The tissue distribution indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, multiple sclerosis, cystic fibrosis, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate

their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene is expressed primarily in immune cells, brain, fetal tissue, and cancerous tissues (such as testes, stomach, lung, pancreas, ovaries) and to a lesser extent in other numerous tissues including, but not limited to, testes and kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and immune cells expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 146 as residues: Lys-23 to Lys-35, Met-46 to Tyr-52. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurodegenerative disorders of the frontal cortex, as well as, cancer or a number of tissues including but not limited to testes, stomach, lung, pancreas, and ovaries.

The tissue distribution indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

The tissue distribution indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility,

lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 44

This gene is expressed primarily in epithelioid sarcoma and to a lesser extent in pancreatic carcinoma, aorta endothelial cells induced with TNF-alpha, and amniotic cells induced with TNF. This gene is also expressed, to a lesser extent, in cancerous lung and ovary tissue and fetal tissue.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, epithelioid sarcoma and related cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., amniotic, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 147 as residues: Tyr-39 to Arg-51. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of certain cancers, including epithelioid sarcoma and pancreatic carcinoma. The tissue distribution in tumors of lung, ovary, and pancreas origins indicates that polynucleotides and

polypeptides corresponding to this gene are useful for the diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated.

Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation.

The tissue distribution indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the

treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: PPVPPWISLPLTGSPPRPGFVPVSPFCFSPMTNGHQVLLLLLLTSAVAAGPWPQ VHAGQWGWMCLPPGLPSVQARSGLGGLPGGPQWVPGGARGY (SEQ ID NO: 237). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for

example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal and infant tissue, particularly infant brain and fetal liver/spleen libraries, and to a lesser extent in breast, ovary tumor, pharynx carcinoma, endometrial stromal cells, thymus, islet cell tumors, and adult cerebellum.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of thc tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, developmental, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in developing cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer and other proliferative disorders. The expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere

herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

IQQWGDSVLGRRCRDLLLQLYLQRPELRVPVPEVLLHSEGAASSSVCKLDGLI
HRFITLLADTSDSRALENRGADASMACRKLAVAHPLLLLRHLPMIAALLHGR
THLNFQEFRQQNHLSCFLHVLGLLELLQPHVFRSEHQGALWDCLLSFIRLLLN

YRKSSRHLAAFINKFVQFIHKYITYNAPAAISFLQKHADPLHDLSFDNSDLVM
LKSLLAGLSLPSRDDRTDRGLDEEGEEESSAGSLPLVSVSLFTPLTAAEMAPY
MKRLSRGQTVEDLLEVLSDIDEMSRRRPEILSFFSTNLQRLMSSAEECCRNLA
FSLALRSMQNSPSIAAAFLPTFMYCLGSQDFEVVQTALRNLPEYALLCQEHA
AVLLHRAFLVGMYGQMDPSAQISEALRILHMEAVM (SEQ ID NO: 238).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in breast cancer, and to a lesser extent in a variety of other cancers, including uterine cancer, synovial sarcoma, and pharynx carcinoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer; proliferative diseases and/or disroders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, breast, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, breast milk, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 149 as residues: Glu-35 to His-41, Ser-62 to Ala-67, Pro-145 to Leu-155, Glu-157 to Ser-163, Arg-190 to Val-197, Asp-208 to Pro-215, Ser-247 to Pro-252. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in breast cancer tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of cancer. Elevated expression of this gene product in cancers, such as

breast cancer, suggest that it may be involved in the abnormal proliferation of cells, dedifferentiation, angiogenesis, and other processes that accompany the development of cancer. Thus, therapeutics targeted against this gene product may be useful therapeutic products in and of themselves. Alternately, expression of this gene product at elevated levels in breast tissue may be reflective of expression within breast lymph nodes, and may suggest a hematopoietic role for this protein. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene shares limited sequence homology with cytochrome-c oxidase.

An alternative embodiment would be the polypeptide comprising, or alternatively consisting of, the following amino acid sequence: MLLKHLQRMVSVPQVKASALKVVTLTANDKTSVSFSSLPGQGVIYNVIVWD PFLNTSAAYIPAHTYACSFEAGEGSCASLGRVSSKVFFTLFALLGFFICFFGHR FWKTELFFIGFIIMGFFFYILITRLTPIKYDVNLILTAVTGSVGGMFLVAVWWR FGILSICMLCVGLVLGFLISSVTFFTPLGNLKIFHDDGVFWVTFSCIAILIPVVF MGCLRILNILTCGVIGSYSVVLAIDSYWSTSLSYITLNVLKRALNKDFHRAFTN VPFQTNDFIILAVWGMLAVSGITLQIRRERGRPFFPPHPYKLWKQERERRVTNI LDPSYHIPPLRERLYGRLTQIKGLFQKEQPAGERTPLLL (SEQ ID NO: 239). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: WARLRGPGAHARTSPQPWRGPSPAQAAMGFLQLLVVXVLXSEHRVAGAAE VFGNSSEGLIEFSVGKFRYF ELNRPFPEEAILHDISSNVTFLIFQIHSQYQNTTVSFSPRRRSPTM (SEQ ID NO: 240). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in keratinocytes, brain, and spinal cord and to a lesser extent in hematopoietic cells and tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders; hematopoietic disorders; integumentary disroders; immune dysfunction; learning disabilities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary, neural, developmental, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and spinal cord cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of neurological and hematopoietic disorders. For example, elevated levels of expression of this gene product in brain and spinal cord indicates that it may be involved in neurodegenerative disorders. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive

disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

Alternately, expression of this gene product in hematopoietic cells indicates that it may be involved in the proliferation, differentiation, survival, and activation of all hematopoietic lineages, including stem and progenitor cells. Expression of this gene product in keratinocytes indicates that it may be involved in normal skin function, and could be involved in skin disorders, dermatitis, and fibrosis. The protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e.wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, uticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, althletes foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chrondomalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, amd chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 48

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: PRVRPASPPVRSPARWGSMAGSPLLWGPRAGGVGLLVLLLLGLFRPPPALCA RPVKEPRGLSAASPPLARLALLAASGGQCPEVRRRGRCRPGAGAGASAGAER QERARAEAQRLRISRRASWRSCCASGAPPATLIRLW AWTTTPTRLQRSSLALCSAPALTLPP (SEQ ID NO: 241). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human pituitary and to a lesser extent in pineal gland, and other areas of the brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pituitary dysfunction; abnormal growth; neurological defects; insufficient milk secretion; abnormal smooth muscle contraction. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of

disorders of the above tissues or cells, particularly of the endocrine and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, breast milk, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 151 as residues: Pro-36 to Gly-42, Pro-64 to Ala-76, Gly-83 to Ala-90, Ser-100 to Cys-108, Thr-126 to Ser-135. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution primarily in pituitary cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of disorders. Elevated expression of this gene product in the pituitary indicates that it may be possibly a hormone-like substance that either controls pituitary development itself, or various processes controlled by the pituitary. These include growth, milk secretion, smooth muscle contraction, diuresis, blood pressure, and homeostasis. Thus, this gene product may have numerous clinical applications. Expression of this gene product in other regions of the brain also indicates that it may be involved in normal neurological function, and may be useful in the treatment of a variety of neurological disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-,hypoparathyroidism) , hypothallamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to

isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: PRVRLATPNIWDLSMLFAFISLLVMLPTWWIVSSWLVWGVILFVYLVIRALRL WRTAKLQVTLKKYSVHLEDMATNSRAFTNLVRKALRLIQETEVISRGFTLVS AACPFNKAGQHPSQHLIGLRKAVYRTLRANFQAARLATLYMLKNYPLNSES DNVTNYICVVPFKELGLGLSEEQISEEEAHNFTDGFSLPALKVLFQLWVAQSS EFFRRLALLLSTANSPPGPLLTPALLPHRILSDVTQGLPHAHSACLEELKRSYE FYRYFETQHQSVPQCLSKTQQKSRELNNVHTAVRSLQLHLKALLNEVIILEDE LEKLVCTKETQELVSEAYPILEQKLKLIQPHVQASNNCWEEAISQVDKLLRRN TDKKGKPEIACENPHCTVSTFEAAYSTHCRQRSNPRGAGIRSLCR (SEQ ID NO: 242). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 7 - 23 of the amino acid sequence referenced in Table 1A for this gene. Moreover, a cytoplasmic tail encompassing amino acids 24 to 390 of this protein has also been determined. Based upon these characteristics, it is

believed that the protein product of this gene shares structural features to type Ib membrane proteins.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in prostate and placenta and to a lesser extent in pancreatic tumors and hematopoietic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer; pancreatic cancer; prostate dysfunction; hematopoietic disorders; reproductive diseases and/or disorders, and pancreatitis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, prostate, pancreas, placental, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 152 as residues: Pro-85 to Ser-94, Pro-127 to Thr-136, Glu-154 to Glu-160, Phe-240 to Ser-250, Leu-255 to Leu-265, Leu-341 to Lys-351, Thr-372 to Gly-384. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in prostate and placental cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of reproductive disorders. Elevated expression of this gene product in the prostate indicates that it may be involved in normal

prostate function, and may be a diagnostic marker for prostate cancer. Alternately, expression of this gene product in placenta indicates that it may play a role in normal vascular function, and may be involved in such processes as angiogenesis and endothelial cell chemotaxis. Thus, this gene product may be useful in the treatment of myocardial infarction, cancer, ischemia, and diabetic retinopathy.

Expression of this gene product in placenta may also be indicative of fetal health and development. Similarly, expression of this gene product in hematopoietic cells indicates that it may be involved in the proliferation, differentiation, survival, or activation of all hematopoietic cell lineages. Finally, expression of this gene product in pancreatic cancers indicates that it may play a role in cancer in general, or in pancreatic function. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

When tested against Jurkat and K562 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) and ISRE (interferon-sensitive responsive element) promoter elements, respectively. Thus, it is likely that this gene activates myeloid, leukemia, and to a lesser extent, other immune or hematopoietic cells and tissue cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. ISRE is also a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: AAPHPPLLRPLCLWCPLWPAWPLRGRPRSAWKRWPPLPVGPAKLGCSMTTR QPTAVSWPCWLMSSSLSTACLAWTLTGSLAREATRRARSLSPTWNCSARQV PPSPPHSGLGRRGWAHCHLT CLLVTQLFRVGRIHPILSLPLVT (SEQ ID NO: 243). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by

the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain and placenta.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular diseases; aberrant angiogenesis; neurological disorders; learning disorders; placental insufficiency; and fetal distress. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular and neurological systems (CNS/PNS), expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 153 as residues: Met-1 to Thr-7, Glu-36 to Ser-43, Pro-46 to Gly-63. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in brain and placental cells and tissues, combined with the detected GAS and ISRE biological activities, indicates that the protein products of this clone are useful for the diagnosis and/or treatment of a variety of neural, reproductive, and vascular diseases and/or disorders. neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis,

encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

Expression of this gene product in placenta indicates that it may play a role in blood vessel development or function, as the placenta is a highly vascularized organ. Thus, this gene product may be involved in such processes as angiogenesis, endothelial cell chemotaxis, and vascular cord formation. Thus, it may be useful in the treatment of such conditions as myocardial infarction; ischemia; and cancer. Alternately, expression of this gene product in the brain indicates that it may play a role in the survival, proliferation, or function of neurons, and thus may be useful in the diagnosis and treatment of such neurological disorders as ALS, schizophrenia, and Alzheimer's disease. It may likewise be involved in learning disorders as well. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: LQLASQSAGIKGMSHCARPTFLTLLLASCFWAAAIPNRNVILSVSFRPLHMQ

FTLSILVFILRILILLRSFL (SEQ ID NO: 244). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 40 - 56 of the amino acid sequence referenced in Table 1A for this gene. Moreover, a cytoplasmic tail encompassing amino acids 57 to 60 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in spleen derived from patients with chronic lymphocytic leukemia.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic lymphocytic leukemia; hematopoietic disorders; impaired immune function; cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in spleen cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of hematopoietic disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Elevated expression of this protein in the spleens of patients with CLL indicates that it may be a useful marker for this disease.

Alternately, it may be associated with the development and/or progression of the disease, and may be a useful target for therapeutic intervention. Additionally, this gene product may play more general roles in hematopoiesis, and may serve to control cellular decisions regarding proliferation, survival, activation, and/or differentiation of all hematopoietic cell lineages. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

The translation product of this gene shares sequence homology with a putative protein tyrosine kinase from the Chilo iridescent virus. See, for example, Genbank accession no. gi|2738451 (AF003534). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities

with tyrosine kinases and signaling proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed in a variety of tissues, including microvascular endothelial cells, dendritic cells, and fetal tissues. as well as several tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, vascular, immune, and developmental diseases and/or disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, immune, developmental, proliferative, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 155 as residues: Ala-21 to Lys-31, Arg-41 to Cys-56, Thr-92 to Cys-102, Arg-132 to Val-137, Lys-152 to Ile-159, Pro-199 to Ser-205, Arg-210 to Asp-219, Ser-225 to Lys-230, Tyr-236 to Ala-241, Lys-243 to Leu-249, Thr-375 to Asp-381. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution and homology to a tyrosine kinase indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved

in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 53

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

The translation product of this gene shares some homology with IL-6DPB (a nuclear, leucine-zipper containing, transcriptional regulator protein involved in interleukin-6 signal transduction); see GenBank Accession GI:204918 (all references available through this accession are hereby incorporated herein by reference; for example Roll, V. et al., Cell 63, 643-653 (1990). Therefore, this gene product is expected to have at least some biological activities in common with transcriptional regulatory proteins.

This gene is expressed primarily in neutrophils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 156 as residues: Gly-63 to Ser-72. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker for neutrophil monitoring in cancer and/or immune suppressed patients and/or during chemotherapy or radiation therapy. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

This gene is expressed primarily in IL-1 and LPS induced neutrophils, and to a lesser extent, in fetal brain.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, and neural diseases and/or disorders, particularly cancer and immune suppression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 157 as residues: Ile-28 to Trp-37, Ser-68 to Lys-81. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a marker in neutrophils to monitor patients who are immune suppressed or cancer patients during chemotherapy or radiation therapy. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune

responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

This gene is expressed primarily in prostate.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, urogenital diseases and/or disorders, particularly prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urogenital system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., urogenital, prostate, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 158 as residues: Arg-30 to Gln-36. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in prostate cancer cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for study, treatment and diagnosis of prostate cancer and other urogenital disorders. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and

conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

A preferred polypeptide of the invention comprises the following amino acid sequence:
MVLVLRHPLCARERAFREPGRGLLTRTGQHDGAPAVTAVPGPLGAVAAAEG
RRSAWGAGGSSPPRKVLWGDMRGRRAGVDVLGPALSSEAAGAEARGWGM
PGMGVGVGASETRGALFLGREGVHGPCPMDGLGPWPWGPW (SEQ ID NO: 245). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in rejected kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the kidney. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., urogenital, renal, kidney, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 159 as residues: Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in kidney indicates the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritus, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. The protein is useful for modulating the immune response to aberrant proteins, as may exist in proliferating cells and tissues. Such modulation of the immune response would also show utility in inhibiting the rejection of transplanted tissues, particularly of the renal system. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

The translation product of this gene shares sequence homology with both human and mouse Fibulin polypeptides which is are extracellular matrix proteins found in heart tissue (See Genbank Accession Nos. emb|CAA57876.1 and emb|CAA53040.1, respectively; all references available through these accessions are hereby incorporated herein by reference; for example, J. Cell Biol. 123 (5), 1269-1277 (1993)).

Preferred polypeptides encoded by this clone comprise, or alternatively consists of, the following amino acid sequence:
MGPAVKMWTNAWKGLDDCHYNQLCENTPGGHRCSCPRGYRMQGPSLPCL
DVNECLQLPKACAYQCHNLQGSYRCLCPPGQTLLRDGKACTSLERNGQNVT
TVSHRGPLLPWLRPWASIPGTSYHAWVSLRPGPMALSSVGRAWCPPGFIRQN
GVCTDLDECRVRNLCQHACRNTEGSYQCLCPAGYRLLPSGKNCQDINECEEE
SIECGPGQMCFNTRGSYQCVDTPCPATYRQGPSPGTCFRRCSQDCGTGGPSTL
QYRLLPLPLGVRAHHDVARLTAFSEVGVPANRTELSMLEPDPRSPFALRPLRA
GLGAVYTRRALTRAGLYRLTVRAAAPRHQSVFVLLIAVSPYPY (SEQ ID NO: 246). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence:
MRVLVVTIAPIYWALARESGEALNGHSLTGGKFRQSHTWSLLQGAAHDDPV
ARGLDPDGLLLLDVVVNGVVPGRAWLTQIFKCRTLKKHYVQTRAWPAVRG

LHTALLPGRPPLVPTLQPQHPVQRGPGPPAPAGAAPAGLSYQLGL (SEQ ID NO: 247). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: HASGAFLVVRGEPQGSWGSMTGVINGRKFGVATLNTSVMQEAHSGVSSIHSS IRHVPANVGPLMRVLVVTIAPIYWALARESGEALNGHSLTGGKFRQESHVEF ATGELLTMTQWPGVWIPMASCSSTWWSMALSPDSLADADLQVQDFEEHYV QTGPGQLFVGSTQRFFQGGLPSFLRCNHSIQYNAARGPQPQLVQHLRASAISS AFDPEAEALRFQLATALQAEENEVGCPEGFELDSQGAFCVDVDECAWDAHL CREGQRCVNLLGSYRCLPDCGPGFRVADGAGCEDVDECLEGLDDCHYNQLC ENTPGGHRCSCPRGYRMQGPSLPCLDVNECLQLPKACAYQC HNLQGSYRCLCPPGQTLLRDGKACTSLERNGQNVTTVSHRGPLLPWLRPWA SIPGTSYHAWVSLRPGPMALSSVGRAWCPPGFIRQNGVCTDLDECRVRNLCQ HACRNTEGSYQCLCPAGYRLLPSGKNCQDINECEEESIECGPGQMCFNTRGS YQCVDTPCPATYRQGPSPGTCFRRCSQDCGTGGPSTLQYRLLPLPLGVRAHH DVARLTAFSEVGVPANRTELSMLEPDPRSPFALRPLRAGLGAVYTRRALTRA GLYRLTVRAAAPRHQSVFVLLIAVSPYPY (SEQ ID NO: 248). Polynucleotides encoding these polypeptides are also encompassed by the invention.

When tested against U937 and Jurkat cell lines, supernatants removed from cells containing this gene repeatedly activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid, T-cells, and to a lesser extent, other immune and hematopoietic cells and tissue cell types, through the

JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in kidney.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the kidney and renal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary tract, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, urogenital, kidney, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 160 as residues: Lys-32 to Ser-37, His-89 to Gly-94, Asn-124 to Gln-130, Ala-163 to Val-168, Cys-196 to Arg-201, Gln-244 to Gln-264, His-288 to Tyr-294, Leu-314 to Gln-319, Ala-392 to Ser-399, Pro-412 to Asp-419, Ala-452 to Pro-460, Arg-466 to Thr-473. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in rejected kidney, the homology to the conserved Fibulin-2 protein, in addition to the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for the

diagnosis and treatment of disorders affecting kidneys, particularly proliferative disorders. Representative uses are described here and elsewhere herein.

The protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritus, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

Preferred polypeptides encoded by this gene comprise, or alternatively consist of, the following amino acid sequence:

MGEKFLLLAMKENHPECFCKILKILHCMDPGEWLPQTEHCVHLTPKEFLIWT MDIASNERSEIQSVALRLASKVISHHMQTCVENRELIAAELKQWVQLVILSCE DHLPTESRLAVVEVLTSTTPLFLTNPHPILELQDTLALWKCVLTLLQSEEQAV RDAATETVTTAMSQENTCQSTEFAFCQVDASIALALALAVLCDLLQQWDQL APGLPILLGWLLG

ESDDLVACVESMHQVEEDYLFEKAEVNFWAETLIFVKYLCKHLFCLLSKSG WRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTVEFTRLRIQEERTL ACLRLLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAAC (SEQ ID NO: 249). Polynucleotides encoding such polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

A preferred polypeptide fragment of the invention comprises the following amino acid sequence:
MGEPNRHPSMFLLLLVLERLYASPMDGTSSALSMGPFVPFIMRCGHSPVYHS
REMAARALVPFVMIDHIPNTIRTLLSTLPSCTDQCFRAKPHSWGHFSRFFHLL
QAYSDSKTRNEFRLPARAD (SEQ ID NO: 250). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
MTGREFFSRFPELYPFLLKQLETVANTVDSDMGEPNRHPSMFLLLLVLERLY
ASPMDGTSSALSMGPFVPFIMRCGHSPVYHSREMAARALVPFVMIDHIPNTIR
TLLSTLPSCTDQCFRQNHIHGTLLQVFHLLQAYSDSKHGTNSDFQHELTDITV
CTKAKLWLAKRQNPCLVTRAVYIDILFLLTCCLNRSAKDNQPVLESLGFWEE
VRGIISGSELITGFPWAFKVPGLPQYLQSLTRLAIAAVWAAAAKSGERETNVPI
SFSQLLESAFPEVRSLTLEALLEKFLAAASGLGEKGVPPLLCNMGEKFLLLAM
KENHPECFCKILKILHCMDPGEWLPQTEHCVHLTPKEFLIWTMDIASNERSEIQ
SVALRLASKVISHHMQTCVENRELIAAELKQWVQLVILSCEDHLPTESRLAVV
EVLTSTTPLFLTNPHPILELQDTLALWKCVLTLLQSEEQAVRDAATETVTTAM
SQENTCQSTEFAFCQVDASIALALALAVLCDLLQQWDQLAPGLPILLGWLLG
ESDDLVACVESMHQVEEDYLFEKAEVNFWAETLIFVKYLCKHLFCLLSKSG

WRPPSPEMLCHLQRMVSEQCHLLSQFFRELPPAAEFVKTVEFTRLRIQEERTL ACLRLLAFLEGKEGEDTLVLSVWDSYAESRQLTLPRTEAAC (SEQ ID NO: 251). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 144 - 160, and 462 - 478 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

Included in this invention as a preferred domain is the formate and nitrite transporters domain, which was identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). A number of bacterial and archaebacterial proteins involved in transporting formate or nitrite have been shown [1] to be related: - focA and focB, from Escherichia coli, transporters involved in the bidirectional transport of formate. - fdhC, from Methanobacterium formicicum and thermoformicicum, a probable formate transporter. - nirC, from Escherichia coli and Salmonella typhimurium, a probable nitrite transporter. - Bacillus subtilis hypothetical protein yrhG. - Bacillus subtilis hypothetical protein ywcJ (ipa-48R). These transporters are proteins of about 280 residues and seem to contain six transmembrane regions. As signature patterns, we selected two conserved regions. The first one is located in what seems to be a cytoplasmic loop between the second and third transmembrane domains; the second is part of the fourth transmembrane region. The 70 Kd yeast hypothetical protein YHL008c is highly similar, in its N-terminal section, to the prokaryotic members of this family. The concensus pattern is as follows: [LIVMA]-[LIVMY]-x-G-[GSTA]-[DES]-L-[FI]-[TN]-[GS].

Preferred polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: IISGSELITG (SEQ ID NO: 252). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further preferred are polypeptides comprising the formate and nitrite transporter domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues may be N-terminal or C- terminal to the formate and nitrite transporter domain. Alternatively, the additional contiguous amino acid residues may be both N-terminal and C-terminal to the formate and nitrite transporter domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to formate and nitrite transporter proteins. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with formate and nitrite transporter proteins. Such activities are known in the art, some of which are described elsewhere herein.

It is believed that this gene maps to chromosome 2. Accordingly, polynucleotides derived from this clone are useful in linkage analysis as markers for chromosome 2.

This gene is expressed primarily in cells of the immune system, primarily T-cells and to a lesser extent in spleen, liver, thymus, tonsils, and testis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

immune and hematopoietic diseases and/or disorders, particularly disorders affecting hematopoesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of hematopoetic cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 161 as residues: Gly-2 to Pro-8, Ser-82 to His-92, Tyr-107 to Asp-117, Arg-162 to Pro-169, Ser-224 to Thr-229, Leu-310 to His-315, Ser-333 to Glu-338, Glu-381 to Ser-388, Gln-428 to Ala-433, Met-446 to Thr-455, Ser-548 to Ser-554, Gly-613 to Asp-618, Ser-627 to Gln-633. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in immune cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting hematopoesis, including cancers. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia,

rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

This gene is expressed primarily in bone marrow, CD34 positive cells, and immune cells, including, neutrophils, T-cells, B-cells, macrophages, monocytes, and dendritic cells and to a lesser extent in brain and tonsils.

In one embodiments, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention may comprise, or alternatively consist of the following amino acid sequence: VDGIDKLDIEFLQQFLETHSRGPRLHSPGHASQEATPGANMSSGTELLWPGAA LLVLLGVAASLCVRCSRPGAKRSEKIYQQRSLREDQQSFTGSRTYSLVGQAW PGPLADMAPTRKDKLLQFYPSLEDPASSRYQNFSKGSRHGSEEAYIDPIAMEY YNWGRFSKPPEDDDANSYENVLICKQKTTETGAQQEGIGGLCRGDLSLSLAL KTGPTSGLCPSASPEEDEGI (SEQ ID NO: 253). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide fragments may comprise or alternatively consist of one, two, three, four or more of the following amino acid sequence: ASSRYQNFSKGSRHGSEEAYIDPIA (SEQ ID NO:413), MEYYNWGRFSKPPEDDDANSY (SEQ ID NO: 414), ENVLICKQKTTETGAQQEGIGGLCRGD (SEQ ID NO: 415), VRCSR PGAKRSEKIYQQRSLREDQQSFTGSRTYSLVGQAWPGPLADMAPTRKDKLLQ FYPSLEDPASS (SEQ ID NO: 416) and LSLSLALKTGPTSGLCPSASPEEDEGI (SEQ ID NO: 417). Polynucleotides encoding these polypeptide fragments (SEQ ID NOS: 413, 414, 415, 416, and/or 417), polynucleotides that hybridize to the complementary strand of these polynucleotides (e.g., under the hybridization conditions described herein) are encompassed by the invention, as are the polypeptides encoded by these hybridizing polynucleotides. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, or more of the immunogenic epitopes shown in SEQ ID NO: 162 as residues: Ser-29 to Thr-57, Pro-74 to Lys-79, Pro-85 to Glu-107, Tyr-118 to Tyr-136, Gln-144 to Gln-152, Ala-182 to Glu-188. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also preferred are polypeptides comprising the mature polypeptide which is predicted to consist of residues 26-190 of the foregoing sequence (SEQ ID NO:162), and biologically active fragments of the mature polypeptide (e.g., fragments that stimulate the proliferation of bone marrow CD34+ cells).

Figures 3A-B show the nucleotide (SEQ ID NO:69) and deduced amino acid sequence (SEQ ID NO:162) of this polypeptide.

Figure 4 shows an analysis of the amino acid sequence (SEQ ID NO:162). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. The domains defined by these graphs are contemplated by the present invention.

The data presented in Figure 4 are also represented in tabular form in Table 7. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 4, and Table 7: "Res": amino acid residue of SEQ ID NO:162 and Figures 3A and 3B; "Position": position of the corresponding residue within SEQ ID NO:162 and Figures 3A and 3B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible

regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 4 and/or Table 7, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 7 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 4, but may, as shown in Table 7, be represented or identified by using tabular representations of the data presented in Figure 4. The DNA*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 4 in a tabular format (See Table 7). The tabular format of the data in Figure 4 is used to easily determine specific boundaries of a preferred region. The above-mentioned preferred regions set out in Figure 4 and in Table 7 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figures 3A-B (SEQ ID NO:162). As set out in Figure 4 and in Table 7, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the deposited cDNA or the nucleotide sequence shown in SEQ ID NO:69 is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also

useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO:69. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:69. In this context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, and from about 601 to about 650, and from about 651 to about 700, and from about 701 to about 750, and from about 751 to about 800, and from about 801 to about 850, and from about 851 to about 900, and from about 901 to about 950, and from about 951 to about 1000, and from about 1001 to about 1050, and from about and from about 1051 to about 1100, and from about 1101 to about 1150, and from about 1151 to about 1200, and from about 1201 to about 1250, and from about 1251 to about 1300, and from about 1301 to about 1350, and from about 1351 to about 1400, and from about 1401 to about 1450, and from about 1451 to about 1500, and from about 1501 to about 1551, and from about 1551 to about 1600, and from about 1601 to about 1650, and from about 1651 to about 1700, and from about 1701 to about 1750, and from about 1751 to about 1797 of SEQ ID NO:69, or the complementary strand thereto, or the cDNA contained in the deposited gene. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the

carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant to be a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) or mature-form of the protein. Such functional activities include, but are not limited to, biological activity (e.g., ability to regulate (e.g., stimulate) hematopoiesis *in vitro or in vivo*), antigenicity, and immunogenicity. The functional activity of polypeptides of the invention, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods described herein.

In addition, assays described herein and otherwise known in the art may routinely be applied to measure biological activity of polypeptides and fragments o f the invention, variants derivatives and analogs thereof (e.g., to regulate (e.g., to stimulate or inhibit) hematopoiesis *in vitro or in vivo*). For example, techniques known in the art (such as for example assaying for thymidine incorporation), may be applied or routinely modified to assay for the ability of the compositions of the invention to inhibit proliferation of hematopoietic cells. Other methods will be known to the skilled artisan and are within the scope of the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, etc.) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such

immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence shown in Figure 3A-B (i.e., SEQ ID NO:69), up to the Glu residue at position number 185 and polynucleotides encoding such polypeptides.

Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-190, where m is an integer from 2 to 184, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:162. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: V-26 to I-190; R-27 to I-190; C-28 to I-190; S-29 to I-190; R-30 to I-190; P-31 to I-190; G-32 to I-190; A-33 to I-190; K-34 to I-190; R-35 to I-190; S-36 to I-190; E-37 to I-190; K-38 to I-190; I-39 to I-190; Y-40 to I-190; Q-41 to I-190; Q-42 to I-190; R-43 to I-190; S-44 to I-190; L-45 to I-190; R-46 to I-190; E-47 to I-190; D-48 to I-190; Q-49 to I-190; Q-50 to I-190; S-51 to I-190; F-52 to I-190; T-53 to I-190; G-54 to I-190; S-55 to I-190; R-56 to I-190; T-57 to I-190; Y-58 to I-190; S-59 to I-190; L-60 to I-190; V-61 to I-190; G-62 to I-190; Q-63 to I-190; A-64 to I-190; W-65 to I-190; P-66 to I-190; G-67 to I-190; P-68 to I-190; L-69 to I-190; A-70 to I-190; D-71 to I-190; M-72 to I-190; A-73 to I-190; P-74 to I-190; T-75 to I-190; R-76 to I-190; K-77 to I-190; D-78 to I-190; K-79 to I-190; L-80 to I-190; L-81 to I-190; Q-82 to I-190; F-83 to I-190; Y-84 to I-190; P-85 to I-190; S-86 to I-190; L-87 to I-190; E-88 to I-190; D-89 to I-190; P-90 to I-190; A-91 to I-190; S-92 to I-190; S-93 to I-190; R-94 to I-190; Y-95 to I-190; Q-96 to I-190; N-97 to I-190; F-98 to I-190; S-99 to I-190; K-100 to I-190; G-101 to I-190; S-102 to I-190; R-103 to I-190; H-104 to I-190; G-105 to I-190; S-106 to I-190; E-107 to I-190; E-108 to I-190; A-109 to I-190; Y-110 to I-190; I-111 to I-190; D-112 to I-190; P-113 to I-190; I-114 to I-190; A-115 to I-190; M-116 to I-190; E-117 to I-190; Y-118 to I-190; Y-119 to I-190; N-120 to I-190; W-121 to I-190; G-122 to I-190; R-123 to I-190; F-124 to I-190; S-125 to I-190; K-126 to I-190; P-

127 to I-190; P-128 to I-190; E-129 to I-190; D-130 to I-190; D-131 to I-190; D-132 to I-190; A-133 to I-190; N-134 to I-190; S-135 to I-190; Y-136 to I-190; E-137 to I-190; N-138 to I-190; V-139 to I-190; L-140 to I-190; I-141 to I-190; C-142 to I-190; K-143 to I-190; Q-144 to I-190; K-145 to I-190; T-146 to I-190; T-147 to I-190; E-148 to I-190; T-149 to I-190; G-150 to I-190; A-151 to I-190; Q-152 to I-190; Q-153 to I-190; E-154 to I-190; G-155 to I-190; I-156 to I-190; G-157 to I-190; G-158 to I-190; L-159 to I-190; C-160 to I-190; R-161 to I-190; G-162 to I-190; D-163 to I-190; L-164 to I-190; S-165 to I-190; L-166 to I-190; S-167 to I-190; L-168 to I-190; A-169 to I-190; L-170 to I-190; K-171 to I-190; T-172 to I-190; G-173 to I-190; P-174 to I-190; T-175 to I-190; S-176 to I-190; G-177 to I-190; L-178 to I-190; C-179 to I-190; P-180 to I-190; S-181 to I-190; A-182 to I-190; S-183 to I-190; P-184 to I-190; and E-185 to I-190, of SEQ ID NO:162. Polypeptides encoding these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an mutein with a large number of deleted C-terminal amino acid residues may

retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figure 3A-B (SEQ ID NO:162), as described by the general formula 1-n, where n is an integer from 6 to 184 where n corresponds to the position of amino acid residue identified in SEQ ID NO:162. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: V-26 to G-189; V-26 to E-188; V-26 to D-187; V-26 to E-186; V-26 to E-185; V-26 to P-184; V-26 to S-183; V-26 to A-182; V-26 to S-181; V-26 to P-180; V-26 to C-179; V-26 to L-178; V-26 to G-177; V-26 to S-176; V-26 to T-175; V-26 to P-174; V-26 to G-173; V-26 to T-172; V-26 to K-171; V-26 to L-170; V-26 to A-169; V-26 to L-168; V-26 to S-167; V-26 to L-166; V-26 to S-165; V-26 to L-164; V-26 to D-163; V-26 to G-162; V-26 to R-161; V-26 to C-160; V-26 to L-159; V-26 to G-158; V-26 to G-157; V-26 to I-156; V-26 to G-155; V-26 to E-154; V-26 to Q-153; V-26 to Q-152; V-26 to A-151; V-26 to G-150; V-26 to T-149; V-26 to E-148; V-26 to T-147; V-26 to T-146; V-26 to K-145; V-26 to Q-144; V-26 to K-143; V-26 to C-142; V-26 to I-141; V-26 to L-140; V-26 to V-139; V-26 to N-138; V-26 to E-137; V-26 to Y-136; V-26 to S-135; V-26 to N-134; V-26 to A-133; V-26 to D-132; V-26 to D-131; V-26 to D-130; V-26 to E-129; V-26 to P-128; V-26 to P-127; V-26 to K-126; V-26 to S-125; V-26 to F-124; V-26 to R-123; V-26 to G-122; V-26 to W-121; V-26 to N-120; V-26 to Y-119; V-26 to Y-118; V-26 to E-117; V-26 to M-116; V-26 to A-115; V-26 to I-114; V-26 to P-113; V-26 to D-112; V-26 to I-111; V-26 to Y-110; V-26 to A-109; V-26 to E-108; V-26 to E-107; V-26 to S-106; V-26 to G-105; V-26 to H-104; V-26 to R-103; V-26 to S-102; V-26 to G-101; V-26 to K-100; V-26 to S-99; V-26 to F-98; V-26 to N-97; V-26 to Q-96; V-26 to Y-95; V-26 to R-94; V-26 to S-93; V-26 to S-92; V-26 to A-91; V-26 to P-90; V-26 to D-89; V-26 to E-88; V-26 to L-87; V-26 to S-86; V-26 to P-85; V-26 to Y-84; V-26 to F-83; V-26 to Q-82; V-26 to L-81; V-26 to L-80; V-26 to K-79; V-26 to D-78; V-26 to K-77; V-26 to R-76; V-26 to T-75; V-26 to P-74; V-26 to A-73; V-26 to M-72; V-26 to D-71; V-26 to A-70; V-26 to L-69; V-26 to P-68; V-26 to G-67; V-26 to P-66; V-26 to W-65; V-26 to A-64; V-26 to Q-63;

V-26 to G-62; V-26 to V-61; V-26 to L-60; V-26 to S-59; V-26 to Y-58; V-26 to T-57; V-26 to R-56; V-26 to S-55; V-26 to G-54; V-26 to T-53; V-26 to F-52; V-26 to S-51; V-26 to Q-50; V-26 to Q-49; V-26 to D-48; V-26 to E-47; V-26 to R-46; V-26 to L-45; V-26 to S-44; V-26 to R-43; V-26 to Q-42; V-26 to Q-41; V-26 to Y-40; V-26 to I-39; V-26 to K-38; V-26 to E-37; V-26 to S-36; V-26 to R-35; V-26 to K-34; V-26 to A-33; V-26 to G-32; and V-26 to P-31 of SEQ ID NO:162. Polypeptides encoding these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:162, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also included are a nucleotide sequence encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209889, where this portion excludes any integer of amino acid residues from 1 to about 184 amino acids from the amino terminus of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209889, or any integer of amino acid residues from 1 to about 190 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209889. Polynucleotides encoding all of the above deletion mutant polypeptide forms also are provided.

The present application is also directed to proteins containing polypeptides at

least 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the polypeptide sequence set forth herein m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune and hematopoietic systems, particularly hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and hematopoeitic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

This gene has been found to stimulate the proliferation of bone marrow CD34+ cells. This assay which is described in Example 53 herein is based on the ability of human CD34+ to proliferate in presence of hematopoietic growth factors and evaluates the ability of the polypeptides of the invention, and agonists and antagonists thereof, to stimulate or inhibit this proliferation.

The tissue distribution in immune and hematopoietic cells and tissues and the ability to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the

proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Moreover, the protein represents a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The polynucleotides and/or polypeptides of the invention and/or agonists and/or antagonists thereof, can also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

The polynucleotides and/or polypeptides of the invention and/or agonists and/or antagonists thereof, may also be employed for the expansion of immature hematopoietic progenitor cells, for example, granulocytes, macrophages or monocytes, by temporarily preventing their differentiation. These bone marrow cells may be cultured *in vitro*. Thus, polynucleotides and/or polypeptides of the invention, or agonists or antagonists thereof, may be useful as a modulator of hematopoietic stem cells *in vitro* for the purpose of bone marrow transplantation and/or gene therapy. Since stem cells are rare and are most useful for introducing genes into for gene therapy, polynucleotides and/or polypeptides of the invention can be used to isolate enriched populations of stem cells. Stem cells can be enriched by culturing cells in the presence of cytotoxins, such as 5-Fu, which kills rapidly dividing cells, where as the stem cells will be protected by polynucleotides and/or polypeptides of the invention. These stem cells can be returned to a bone marrow transplant patient or can then be used for transfection of the desired gene for gene therapy. In addition, this gene can be injected into animals which results in the release of stem cells from the bone marrow of the animal into the peripheral blood. These stem cells can be isolated for the purpose of autologous bone marrow transplantation or manipulation for gene therapy. After the patient has finished chemotherapy or radiation treatment, the isolated stem cells can be returned to the patient.

Polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

This gene product may also be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma.

This gene may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/ immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for

regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Based upon the proteins immune cell specific message distribution, it may be involved in many aspects of the immune response, especially its initial stages, inflammation, allograft rejection, infectious disease response etc. It is frequently found in the hematopoietic cell cDNA libraries. Thus, this factor could be involved in the control of hematopoietic cell proliferation, differentiation, and function. Based on this one can postulate its use in the management of anemias, leukemias, neutropenia, thrombocytopenia, autoimmune diseases, blood tissue engraftment, and poikilothromerythromatosis. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: VLWREASALVLSNRLSSGLLHDLLLQPAIHSRLFPRRSRGLSEGEGSSVSLQRS RVLSA MKHVLNLYLLGVVLTLLSIFVRVMESLEGLLESPSPGTSWTTRSQLANTEPTK GLPDHPSRSM (SEQ ID NO: 259). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement

there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in immune cells including activated T cells, macrophages, jurkat cells, bone marrow cells, and osteoblasts and to a lesser extent in kidney cortex, brain, placenta and lung.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic diseases and/or disorders, particularly inflammation and diseases related to inflammatory activity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 163 as residues: Pro-34 to Met-63. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in immune cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing disease related to the normal or abnormal activation of T cells. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
YTFHTQIFLDFPMIFLTVLPLAFLFLHSGFYHYISFSCLFSLSLALFFFLDVATFR
RPGQLFCERSVLFDMFHFGFVSLFLHEWIQAKHFWAGLFIVLPSDVFFSVHHL

EAPDGSFPNIAKLSLIILLR (SEQ ID NO: 260). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have two transmembrane domains at about amino acid position 2 - 18 and 22 - 38 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

This gene is expressed in many tissues including brain, liver, prostate, testes, cartilage, gall bladder. Expression is also seen in a number of tumors including colon carcinoma, pancreas tumor, osteoclastoma, ovarian cancer, B cell lymphoma and acute lymphocytic leukemias.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors of various organs including the pancreas, colon, and bone. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the major organs, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, hepatic, metabolic, reproductive, testicular, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors and proliferative tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for treating or diagnosing tumors of several major organs including the pancreas and large intestine. This protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

This gene is expressed primarily in dendritic cells and fetal liver/spleen and to a lesser extent in many tissues including tonsils, fetal lung, stromal cell lines, bone marrow cell lines, placenta and tumors including hepatocellular carcinoma, pancreas tumor and osteosarcoma.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune and hematopoietic system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic cells and fetal liver/spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating disorders of the immune system particularly related to the control and generation of precursor cells. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed

progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in adrenal gland tumor and endothelial cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine and vascular diseases and/or disorders, particularly diseases associated with the vascular endothelium. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosing and treating disorders that involve the vascular system including diseases such as atherschlerosis, neoangiogenesis associated with tumor growth and conditons associated with inflammation. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke,

embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Alternatively, the protein is useful in the treatment, detection, and/or prevention of metabolic disorders, particularly lethargy and depression. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

The translation product of this gene is related to bovine PAM precursor. See Genbank record gi|163482 incorporated herein by reference. Moreover, see following patent publications are also incorporated herein by reference: J04311386 and WO8902460. Many bioactive peptides terminate with an amino acid alpha-amide at their COOH terminus. The enzyme responsible for this essential posttranslational modification is known as peptidyl-glycine alpha-amidating monooxygenase or PAM. An NH2-terminal signal sequence and short propeptide precede the NH2 terminus of purified PAM. The sequences of several PAM cyanogen bromide peptides were localized in the NH2-terminal half of the predicted protein. The forms of PAM purified from bovine neurointermediate pituitary may be generated by endoproteolytic cleavage at a subset of the 10 pairs of basic amino acids in the precursor. High levels of PAM mRNA have been found in bovine pituitary and cerebral cortex. In corticotropic tumor cells, levels of PAM mRNA and pro-ACTH/endorphin mRNA are known to be regulated in parallel by glucocorticoids and CRF.

This gene is expressed primarily in endometrial tumors, dendritic cells, a multiple sclerosis library, kidney, hematopoietic cells, melanocytes, osteoblasts, the spleen, colon, ovary, stromal cells, fetal and adult brain, heart, and in tissues undergoing wound repair.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometriosis, endometrial cancer, multiple sclerosis, hematopoietic diseases, bone disease, and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly the hematopoietic system and female reproduction. expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, immune, hematopoieticm integumentary, skeletal, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in dendritic and hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapuetic or diagnostic agent is diseases of hematopoietic origin as well as the female reproductive track due to the gene's primary pattern of expression. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein may also have a very wide range of biological activities. Representative uses are described in

the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the protein may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 65

The translation product of this gene shares sequence similarity with several G-protein coupled receptors (See Genbank Accession No. gb|AAC77910.1| (AF061443); all references available through this accession are hereby incorporated herein by reference; for example, Mol. Endocrinol. 12, 1830-1845 (1998)). G-protein coupled receptors are well known in the are and affect a variety of functions. In particular, the translation product of this gene shares similarity with Follical Stimulating Hormone Receptor.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GTRFPTGETPSLGFTVTLVLLNSLAFLLMAVIYTKLYCNLEKEDLSENSQSSMI KHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFP (SEQ ID NO: 261). Polynucleotides encoding such polypeptides are also encompassed by the

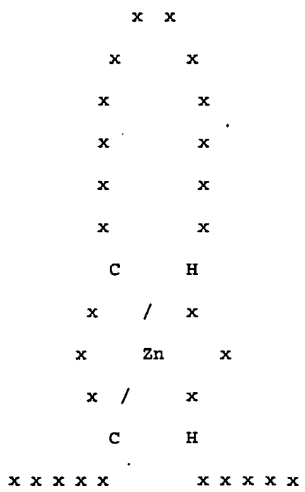
invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: MIKHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFPCLLA (SEQ ID NO: 262). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GTRFPTGETPSLGFTVTLVLLNSLAFLLMAVIYTKLYCNLEKEDLSENSQSSMI KHVAWLIFTNCIFFCPVAFFSFAPLITAISISPEIMKSVTLIFFPLPACLNPVLYVF FNPKFKEDWKLLKRRVTKKSGSVSVSISSQGGCLEQDFYYDCGMYSHLQGN LTVCDCCESFLLTKPVSCKHLIKSHSCPALAVASCQRPEGYWSDCGTQSAHS DYADEEDSFVSDSSDQVQACGRACFYQSRGFPLVRYAYNLPRVKD (SEQ ID NO: 263). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 43 - 59 of the amino acid sequence referenced in Table 1A for this gene. Moreover, a cytoplasmic tail encompassing amino acids 60 to 207 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

Included in this invention as preferred domains are Zinc finger, C2H2 type domains, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). 'Zinc finger' domains [1-5] are nucleic acid-binding protein structures first identified in the Xenopus transcription factor TFIIIA. These domains have since been found in numerous nucleic acid-binding proteins. A zinc finger domain is composed of 25 to 30 amino-acid residues. There are two cysteine or histidine residues at both extremities of the domain, which are involved in the tetrahedral coordination of a zinc atom. It has been proposed that such a domain interacts with about five nucleotides. A schematic representation of a zinc finger domain is shown below:



Many classes of zinc fingers are characterized according to the number and positions of the histidine and cysteine residues involved in the zinc atom coordination. In the first class to be characterized, called C2H2, the first pair of zinc coordinating residues are cysteines, while the second pair are histidines. A number of experimental reports have demonstrated the zinc- dependent DNA or RNA binding property of some members of this class. Some of the proteins known to include C2H2-type zinc fingers are listed below. We have indicated, between brackets, the number of zinc finger regions found in each of these proteins; a '+' symbol indicates that only partial sequence data is available and that additional finger domains may be present. In addition to the conserved zinc ligand residues it has been shown that a number of other positions are also important for the structural integrity of the C2H2 zinc fingers. The best conserved position is found four residues after the second cysteine; it is generally an aromatic or aliphatic residue. The concensus pattern is as follows: C-x(2,4)-C-x(3)-[LIVMFYWC]-x(8)-H-x(3,5)-H. Preferred polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: CDCCESFLLTKPVSCKHLIKSH (SEQ ID NO: 264). Polynucleotides encoding these polypeptides are also encompassed by the invention. Further preferred are polypeptides comprising the Zinc finger, C2H2 type domain of the sequence referenced in Table for this gene, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of this referenced sequence. The additional contiguous amino acid residues may be N-terminal or C- terminal to the Zinc finger, C2H2 type domain. Alternatively, the additional contiguous amino acid residues may be both N-terminal and C-terminal to the Zinc finger, C2H2 type domain, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number. The above preferred polypeptide domain is characteristic of a signature specific to zinc finger proteins. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with G-coupled proteins, their receptors, and zinc finger proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in adult and fetal liver, human placenta, colon carcinoma cell lines and fibroblasts and to a lesser extent in the fetal and adult brain, the developing nervous system, lung, pancreas, salivary gland, breast tissue, and dendritic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the liver, developmental abnormalities, neurologic diseases, lung cancer, pancreatic cancer, and colon cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and hepatic origin, as well as the proliferation and/or differentiation of numerous types of tissues. expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, immune, hematopoietic, neural, gastrointestinal, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 168 as residues: Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in fetal liver indicates that polynucleotides and polypeptides corresponding to this gene are useful for a diagnostic marker or therapeutic in a wide variety of disease states. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in

Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Alternatively, the protein expression in placental and brain tissue indicates the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. The protein is useful in the treatment, detection, and/or prevention of bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; pain; cancers; anorexia; bulimia; asthma; Parkinson's disease; acute heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ulcers; allergies; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 66

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: ALENSGSPGLQDSARAHFNXSLRSFSFLRNQMYIFELSLYLEGTSFVVVLLFLL ISVSLDSPPTTKGWDS VLHIWVPLIVQ (SEQ ID NO: 265). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placenta and in hematopoietic cells, especially those of T-cell and monocyte origin and to a lesser extent in the brain, endothelial cells, and the lungs.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, vascular, and developmental diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 169 as residues: Ser-30 to Trp-37. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in hematopoietic cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic intervention in hematopoietic and developmental disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs or regulates the survival of neighboring neurons. Likewise, it is involved in controlling the digestive process, and such actions as peristalsis. Similarly, it is involved in controlling the vasculature in areas where smooth muscle surrounds the endothelium of blood vessels. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 67

This gene is expressed primarily in the prostate and to a lesser extent in human B-cell lymphomas.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer and diseases of hematopoietic origin, particularly of B-cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., prostate, reproductive, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 170 as residues: Asp-33 to Lys-42. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in prostate tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic or diagnostic marker for prostate cancer and disorders involving hematopoietic cells, especially those of B-cell origin. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders"

and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. The protein is useful in modulating the immune response to aberrant proteins and polypeptides, as may exist in rapidly proliferating cells and tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 68

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of

many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: GHESICGSCRSWIYFSIRCRRRMRPWWSLLLEACATCAQTGPTRSTSCTQEVS HSSSTAYPAPMRRRCCLPSPRSCT (SEQ ID NO: 266). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

This gene is expressed primarily in the brain and the developing embryo and to a lesser extent in the heart, colon, adipose tissue, kidney, mammary tissue, activated T-cells and dendritic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological diseases, developmental conditions, colon cancer, and hematopoietic diseases, especially of T-cell origin . Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, cardiovascular, adipose, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 171 as residues: Thr-18 to Cys-26, Glu-29 to Thr-36, Ser-50 to Thr-55. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in brain, combined with the detected GAS biological activity, indicates that polynucleotides and polypeptides corresponding to this gene are useful for therapeutic and/or diagnostic agents in neurological diseases, developmental abnormalities, colon cancer, and hematopoietic diseases, especially those of T-cell origin. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or

receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 69

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 - 18 of the amino acid sequence referenced in Table 1A for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: KRAGVEVGGLVMALAGSVFVLGGVLVLCVERNGEGEMGWPQHLPKSQPLS PPVAVRRCSFERSWIDLLVETSSSMVTCRQQVGTPNGMEGRGGGPKTTFPIRL QLSGACAVRPEIQWEV (SEQ ID NO: 267). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated monocytes, dendritic cells, and in the tonsils.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to,

immune and hematopoietic diseases and/or disorders, particularly leukemia, lymphomas, tumors of hematopoietic origin. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 172 as residues: Gln-30 to Leu-38, Asn-75 to Thr-86. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution in activated monocytes, dendritic cells, and tonsils indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic and/or diagnostic agent for leukemias, lymphomas, and other diseases associated with cells of hematopoietic origin. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to

transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 70

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune cells and tissue cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

This gene is expressed primarily in the placenta, brain, and liver and to a lesser extent in most other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic, neurological, vascular, and developmental diseases and/or disorders, particularly cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, neurological, vascular, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, bile, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful therapeutic and/or diagnostic agent in a multitude of disease states, particularly those involving the immune and neurologic systems. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein is useful in the detection, treatment,

and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 71

The translation product of this gene shares sequence homology with the murine Fig1 (interleukin-four induced gene 1) (See Genbank Accession No AAB51353; all references available through this accession are hereby incorporated herein by reference; for example Chu,C.C. and Paul,W.E., Proc. Natl. Acad. Sci. U.S.A. 94 (6), 2507-2512 (1997)) which shares homology to the monoamine oxidases, particularly in domains responsible for FAD binding.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: QDWKAERSQDPFEKCMQDPDYEQLLKVTILEADNRIGGRIFTYRDQXTGWIG ELGAMRMPSSHRILHKLCQGLGLNLTKFTQYDKNTWTEVHEXKLRNYVVEK VPEKLGYALRPQEKGHSPEDIYQMALNQALKDLKALGCRKAMKKFERHTLL EYLLGEGNLSRPAVQLLGDVMSEDGFFYLSFAEALRAXSCLSDRLQYSRIVG GWDLLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQIETSPPARNLKVLKAD VVLLTASGPAVKRITFS (SEQ ID NO: 268), and/or LPRHMQEALRRLHYVPATKVFLSFRRPFWREEHIEGGHSNTDRPSRMIFYPPP REGALLLASYTWSDAAAAFAGLSREEALRLALDDVAALHGPVVRQLWDGT GVVKRWAEDQHSQGGFVVQXPALWQTEKDDWTVPYGRIYFAGEHTAYPHG WVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVASSPSH DLAKEEGS (SEQ ID NO: 269). Polynucleotides encoding such polypeptides are also encompassed by the invention. Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence: MAPLALHLLVLVPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVTILE ADNRIGGRIFTYRDQXTGWIGELGAMRMPSSHRILHKLCQGLGLNLTKFTQY DKNTWTEVHEXKLRNYVVEKVPEKLGYALRPQEKGHSPEDIYQMALNQAL KDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDVMSEDGFFYLS FAEALRAXSCLSDRLQYSRIVGGWDLLPRALLSSLSGLVLLNAPVVAMTQGP HDVHVQIETSPPARNLKVLKADVVLLTASGPAVKRITFSPRCPATCRRRCGGC TTCRPPRCS (SEQ ID NO: 270). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides , or the complement there of are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with monoamine oxidases, disintegrins, metalloproteinases, and apoptosis modulating proteins. Such activities are known in the art, some of which are described elsewhere herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 235 - 251 of the amino acid sequence referenced in Table 1A for this gene. Moreover, a cytoplasmic tail encompassing amino acids 252 to 319 of this protein has also been determined. Based upon these characteristics,

it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in hematopoietic cells, particularly in dendritic cells, and activated monocytes and to a lesser extent in T-cells, endothelial cells, and cells associated with ulcerative colitis.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemias, lymphomas, and diseases associated with antigen presenting cells, in addition to apoptosis dependant events. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 174 as residues: Gln-22 to Gln-44, Ala-90 to Gly-95, Lys-137 to Trp-146, Arg-171 to Asp-181, Glu-370 to Ser-380, Asp-447 to Gly-452, Gln-463 to Trp-469, Asn-504 to Ala-510, Asp-512 to His-519, Ala-541 to Val-550, Asn-558 to His-566. Polynucleotides encoding said polypeptides are also encompassed by the invention. Antibodies that bind said epitopes or other polypeptides of the invention are also encompassed.

The tissue distribution immune and hematopoietic cells and tissues, combined with the homology to the murine Fig 1 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful as a therapeutic and/or diagnostic agent for hematopoietic diseases, especially those associated with antigen presenting cells. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere

herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Table 1A

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HISCN02	209878 05/18/98	pSport1	11	1113	1	1113	232	232	104	1	26	27	106
2	HHGDM70	209878 05/18/98	Lambda ZAP II	12	983	102	983	69	69	105	1	57	58	86
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	13	973	1	973	68	68	106	1	37	38	302
3	HHPGO40	209878 05/18/98	Uni-ZAP XR	82	984	1	984	74	74	175	1	37	38	224
4	HAMGG68	209878 05/18/98	pCMVSport 3.0	14	1458	1	1458	312	312	107	1	20	21	55
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	15	2005	1	2005	251	251	108	1	22	23	189
5	HAPOM49	209878 05/18/98	Uni-ZAP XR	83	2664	1	2664	448	448	176	1	1	2	123
6	HBGBA69	209878 05/18/98	Uni-ZAP XR	16	943	1	933	62	62	109	1	38	39	60
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	17	1503	588	1480	290	290	110	1	26	27	128

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
7	HBJFJ26	209878 05/18/98	Uni-ZAP XR	84	1328	413	1305	591	591	177	1	20	21	59
8	HCEDH38	209878 05/18/98	Uni-ZAP XR	18	1512	1	1438	222	222	111	1	26	27	68
9	HDPOJ08	209878 05/18/98	pCMVSport 3.0	19	1655	1	1655	159	159	112	1	18	19	122
10	HDPRX82	209878 05/18/98	pCMVSport 3.0	20	2525	1	2525	128	128	113	1	32	33	82
11	HELGK31	209878 05/18/98 209044 05/15/97	Uni-ZAP XR	21	1396	25	1334	209	209	114	1	29	30	344
11	HCNUA40	97898 02/26/97	pBluescript	85	1342	949	1237	960	960	178	1	33	34	105
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	22	1069	1	1069	181	181	115	1	28	29	181
12	HFPCX64	209878 05/18/98	Uni-ZAP XR	86	1154	84	1154	257	257	179	1	28	29	87
12	HCEBW71	209225 08/28/97	Uni-ZAP XR	87	1197	141	1197	257	257	180	1	28	29	87
13	HFXDO60	209878 05/18/98	Lambda ZAP II	23	1658	1	1658	131	131	116	1	46	47	115

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
14	HHEPG41	209878 05/18/98	pCMVSport 3.0	24	1077	385	1043	514	514	117	1	35	36	70
14	HAUAI83	209626 02/12/98	Uni-ZAP XR	88	910	1	886	253	253	181	1	37	38	49
14	HJPAZ83	209626 02/12/98 97958 03/13/97	Uni-ZAP XR	89	1076	398	1076		575	182	1	11	12	23
15	HKGAH42	209878 05/18/98	pSport1	25	1205	1	1205	143	143	118	1	21	22	63
16	HMIAP86	209878 05/18/98	Uni-ZAP XR	26	1674	13	1674	182	182	119	1	19	20	334
17	HMUAP70	209878 05/18/98	pCMVSport 3.0	27	1965	531	1914	183	183	120	1	16	17	221
17	HMUAP70	209878 05/18/98	pCMVSport 3.0	90	1842	407	1783	413	413	183	1	25	26	103
17	HAGFY16	209626 02/12/98 97923 03/07/97	Uni-ZAP XR	91	1963	209	1922	251	251	184	1	28	29	198
17	HBMCF37	209683 03/20/98	pBluescript	92	1487	79	1487	170	170	185	1	44	45	70

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
17	HFLQB16	209641 02/25/98	Uni-ZAP XR	93	1653	394	1637	413	413	186	1	25	26	82
17	HAGFY16	209626 02/12/98	Uni-ZAP XR	94	1830	87	1786	128	128	187	1	26	27	45
18	HRACJ35	209878 05/18/98	pCMVSport 3.0	28	1863	8	1863	99	99	121	1	24	25	472
18	HAWAZ34	209141 07/09/97	pBluescript SK-	95	1134	472	1132	687	687	188	1			33
19	HTWDE26	209878 05/18/98	pSport1	29	1626	1	1626	68	68	122	1	30	31	167
19	HMHBN40	97901 02/26/97 209047 05/15/97	Uni-ZAP XR	96	1772	69	1772	129	129	189	1	30	31	231
20	HUSIB13	209878 05/18/98	pSport1	30	605	1	605	172	172	123	1	32	33	46
21	HBAFA02	209877 05/18/98	pSport1	31	931	359	931	46	46	124	1	21	22	108
22	H2CBT75	209877 05/18/98	pBluescript SK-	32	1407	1	1407	32	32	125	1	23	24	60
23	HAGDQ42	209877 05/18/98	Uni-ZAP XR	33	1526	1	1526	126	126	126	1	18	19	248

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
24	HBMCJ42	209877 05/18/98	pBluescript	34	1737	41	1580	244	244	127	1	44	45	248
25	HDPBQ71	209877 05/18/98	pCMVSport 3.0	35	2312	1	2312	93	93	128	1	33	34	612
25	HDPBQ71	209877 05/18/98	pCMVSport 3.0	97	2242	6	2242	24	24	190	1	33	34	612
25	HDPFQ90	PTA-499 08/11/99	pCMVSport 3.0	98	2381	162	2381	165	165	191	1	33	34	456
26	HCEJG71	209877 05/18/98	Uni-ZAP XR	36	2235	2	2235	28	28	129	1	25	26	447
27	HELHL48	209877 05/18/98	Uni-ZAP XR	37	2971	560	2557	629	629	130	1	16	17	291
27	HSKCT36	209580 01/14/98	Uni-ZAP XR	99	1955	1	1955	31	31	192	1	18	19	184
28	HISAQ04	209877 05/18/98	pSport1	38	1163	1	1163	61	61	131	1	21	22	78
29	HJACB89	209877 05/18/98	pBluescript SK-	39	1932	28	1930	95	95	132	1	23	24	333
30	HTECC05	209877 05/18/98	Uni-ZAP XR	40	881	1	881	27	27	133	1	15	16	164
31	HBJLF01	209877 05/18/98	Uni-ZAP XR	41	1932	201	1931	217	217	134	1	46	47	244

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HBXGP60	209877 05/18/98	ZAP Express	42	1164	1	1164	143	143	135	1	22	23	55
33	HCE5B20	209877 05/18/98	Uni-ZAP XR	43	1105	1	1105	237	237	136	1	25	26	54
34	HCMSQ56	209877 05/18/98	Uni-ZAP XR	44	1262	1	1262	148	148	137	1	19	20	88
35	HCNAH57	209877 05/18/98	Lambda ZAP II	45	517	1	517	35	35	138	1	33	34	61
36	HCUEP91	209877 05/18/98	ZAP Express	46	858	2	858	266	266	139	1	20	21	105
37	HDPCJ91	209877 05/18/98	pCMVSport 3.0	47	6107	1	6107	131	131	140	1	28	29	51
38	HDPGK25	209877 05/18/98	pCMVSport 3.0	48	703	1	703	345	345	141	1	33	34	119
39	HE2DY70	209877 05/18/98	Uni-ZAP XR	49	639	1	639	137	137	142	1	45	46	58
40	HE2NV57	209877 05/18/98	Uni-ZAP XR	50	867	1	867	99	99	143	1	36	37	99
41	HETBR16	209877 05/18/98	Uni-ZAP XR	51	1569	1	1569	161	161	144	1	21	22	64
42	HFXDG13	209877 05/18/98	Lambda ZAP II	52	1196	1	1196	43	43	145	1	37	38	66

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
43	HFXKY27	209877 05/18/98	Lambda ZAP II	53	945	1	945	44	44	146	1	19	20	58
44	HHPEC09	209877 05/18/98	Uni-ZAP XR	54	488	1	488	71	71	147	1	19	20	55
45	HISAD54	209877 05/18/98	pSport1	55	2860	1	2860	172	172	148	1	19	20	65
46	HJBCY35	209877 05/18/98	pBluescript SK-	56	1559	93	1272	232	232	149	1	23	24	327
47	HKAEA19	209877 05/18/98	pCMVSport 2.0	57	2064	1	1909	83	83	150	1	21	22	89
48	HKGDL36	209877 05/18/98	pSport1	58	1050	1	1050	55	55	151	1	33	34	148
49	HLDBS43	209877 05/18/98	pCMVSport 3.0	59	2533	1	2533	73	73	152	1	26	27	390
50	HLWAD92	209877 05/18/98	pCMVSport 3.0	60	899	1	899	197	197	153	1	34	35	98
51	HLYBI15	209877 05/18/98	pSport1	61	1079	1	1079	92	92	154	1	22	23	60
52	HMEJE05	209889 05/22/98	Lambda ZAP II	62	1928	1	1928	25	25	155	1	30	31	392
53	HNGIX55	209889 05/22/98	Uni-ZAP XR	63	781	1	781	121	121	156	1	19	20	74

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
54	HNHEX30	209889 05/22/98	Uni-ZAP XR	64	1194	1	1194	138	138	157	1	15	16	81
55	HPJBI33	209889 05/22/98	Uni-ZAP XR	65	1677	1	1677	236	236	158	1	31	32	53
56	HRABA80	209889 05/22/98	pCMVSport 3.0	66	1237	1	1237	130	130	159	1	28	29	102
57	HRACD80	209889 05/22/98	pCMVSport 3.0	67	1934	1	1934	191	191	160	1	16	17	575
57	HRACD80	209889 05/22/98	pCMVSport 3.0	100	1958	1	1958	191	191	193	1	16	17	146
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	68	3300	984	2729	677	677	161	1	22	23	643
58	HSLCX03	209889 05/22/98	Uni-ZAP XR	101	2444	1	2444	392	392	194	1	22	23	124
59	HT5GJ57	209889 05/22/98	Uni-ZAP XR	69	1797	92	1797	122	122	162	1	25	26	190
60	HTACS42	209889 05/22/98	Uni-ZAP XR	70	1373	1	1373	213	213	163	1	29	30	63
61	HTEKE40	209889 05/22/98	Uni-ZAP XR	71	1579	1	1579	173	173	164	1	47	48	117
62	HTOBX69	209889 05/22/98	Uni-ZAP XR	72	1028	1	1028	28	28	165	1	20	21	42

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
63	HUVEO77	209889 05/22/98	Uni-ZAP XR	73	3674	1	3674	55	55	166	1	27	28	47
64	H2CBG48	209889 05/22/98	pBluescript SK-	74	2797	1	2797	125	125	167	1	25	26	45
65	H2CBU83	209889 05/22/98	pBluescript SK-	75	2703	1	2703	157	157	168	1	30	31	207
65	H2CBU83	209889 05/22/98	pBluescript SK-	102	2709	1	2709	157	157	195	1	30	31	51
66	HAPNY94	209889 05/22/98	Uni-ZAP XR	76	742	1	742	94	94	169	1	29	30	50
67	HBJHZ58	209889 05/22/98	Uni-ZAP XR	77	1825	1	1825	102	102	170	1	29	30	42
68	HCE2B33	209878 05/18/98	Uni-ZAP XR	78	1674	1	1668	67	67	171	1	18	19	55
69	HDPBQ02	209889 05/22/98	pCMVSport 3.0	79	2191	291	2191	460	460	172	1	24	25	108
70	HFIYI70	209889 05/22/98	pSport1	80	1335	1	1335	43	43	173	1	15	16	50
71	HDPOZ56	209889 05/22/98	pCMVSport 3.0	81	1867	415	1867	103	103	174	1	21	22	566
71	HDPOZ56	209889 05/22/98	pCMVSport 3.0	103	1722	1	1722	59	59	196	1	21	22	319

Table 1B

Gene No:	Clone ID NO: Z	Contig ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Tissue Distribution Library code: count (see Table IV for Library Codes)	Cytologic Band	OMIM Disease Reference(s):
1	HISCN02	638033	11	232 - 549	104		AR183: 9, AR182: 7, AR269: 7, AR180: 6, AR161: 6, AR162: 6, AR163: 5, AR173: 5, AR245: 5, AR270: 5, AR257: 5, AR181: 5, AR171: 5, AR179: 4, AR263: 4, AR238: 4, AR268: 4, AR175: 4, AR296: 4, AR172: 4, AR176: 4, AR178: 4, AR264: 4, AR313: 4, AR165: 4, AR243: 4, AR290: 4, AR164: 4, AR096: 4, AR309: 3, AR300: 3, AR242: 3, AR222: 3, AR166: 3, AR240: 3, AR223: 3, AR293: 3, AR217: 3, AR193: 3, AR261: 3, AR291: 3, AR170: 3, AR311: 3, AR213: 3, AR267: 3, AR195: 3,		

							AR297: 3, AR312: 3, AR266: 3, AR216: 3, AR246: 3, AR234: 3, AR224: 3, AR191: 3, AR247: 3, AR258: 3, AR190: 3, AR294: 3, AR277: 3, AR228: 2, AR177: 2, AR229: 2, AR286: 2, AR196: 2, AR295: 2, AR262: 2, AR237: 2, AR189: 2, AR174: 2, AR299: 2, AR285: 2, AR231: 2, AR188: 2, AR288: 2, AR282: 2, AR274: 2, AR287: 2, AR226: 2, AR227: 2, AR233: 2, AR239: 2, AR289: 2, AR255: 2, AR275: 2, AR089: 2, AR225: 2, AR218: 2, AR055: 2, AR316: 2, AR212: 2, AR210: 2, AR219: 2, AR205: 2, AR260: 2, AR200: 2, AR033: 2, AR236: 2, AR204: 1, AR308: 1, AR199: 1, AR039: 1, AR272: 1, AR185: 1, AR254: 1,		

							AR230: 1, AR060: 1, AR232: 1, AR203: 1, AR192: 1, AR214: 1, AR168: 1, AR256: 1 H0539: 1		
2	HHGDM70	623416	12	69 - 326	105	Gly-29 to Ser-35, Ser-63 to Cys-68.	AR060: 4, AR299: 4, AR283: 2, AR104: 2, AR185: 2, AR316: 2, AR277: 2, AR089: 1, AR313: 1 S0116: 1, H0255: 1 and H0333: 1.		
3	HHPGO40	753270	13	68 - 973	106		AR244: 5, AR202: 5, AR273: 5, AR194: 4, AR176: 4, AR253: 4, AR214: 4, AR206: 4, AR309: 3, AR235: 3, AR186: 3, AR251: 3, AR052: 3, AR222: 3, AR224: 3, AR204: 3, AR282: 3, AR289: 3, AR248: 3, AR215: 3, AR277: 3, AR284: 3, AR181: 3, AR269: 3, AR180: 2, AR312: 2, AR246: 2, AR061: 2, AR182: 2, AR162: 2, AR184: 2, AR163: 2, AR296: 2, AR198: 2,		

							AR161: 2, AR223: 2, AR291: 2, AR298: 2, AR171: 2, AR267: 2, AR229: 2, AR055: 2, AR297: 2, AR225: 2, AR265: 2, AR285: 2, AR193: 2, AR228: 2, AR270: 2, AR292: 2, AR183: 2, AR261: 2, AR033: 2, AR290: 2, AR268: 2, AR169: 2, AR310: 2, AR266: 2, AR271: 2, AR205: 2, AR264: 2, AR286: 2, AR192: 2, AR039: 2, AR247: 2, AR283: 2, AR053: 2, AR240: 2, AR300: 2, AR060: 2, AR287: 2, AR293: 2, AR257: 2, AR096: 2, AR089: 2, AR239: 2, AR104: 2, AR185: 1, AR213: 1, AR178: 1, AR294: 1, AR237: 1, AR299: 1, AR177: 1, AR275: 1, AR288: 1, AR313: 1, AR175: 1, AR238: 1, AR272: 1, AR274: 1, AR173: 1,		

							AR231: 1, AR236: 1, AR233: 1, AR179: 1, AR316: 1, AR259: 1, AR234: 1, AR295: 1, AR230: 1, AR243: 1, AR199: 1 H0521: 17, H0522: 12, S0114: 3, S0116: 3, H0402: 2, H0634: 2, S0440: 2, H0547: 2, S0292: 2, L0756: 2, H0265: 1, H0556: 1, H0686: 1, S0134: 1, S0218: 1, L0785: 1, H0254: 1, H0638: 1, H0637: 1, H0370: 1, H0559: 1, H0490: 1, H0485: 1, H0635: 1, H0581: 1, H0421: 1, H0597: 1, H0620: 1, H0051: 1, H0083: 1, H0252: 1, H0063: 1, H0059: 1, H0625: 1, L0667: 1, L0768: 1, L0653: 1, L0659: 1, L0783: 1, H0702: 1, H0701: 1, H0539: 1, H0518: 1, H0727: 1, L0366: 1, H0543: 1 and		

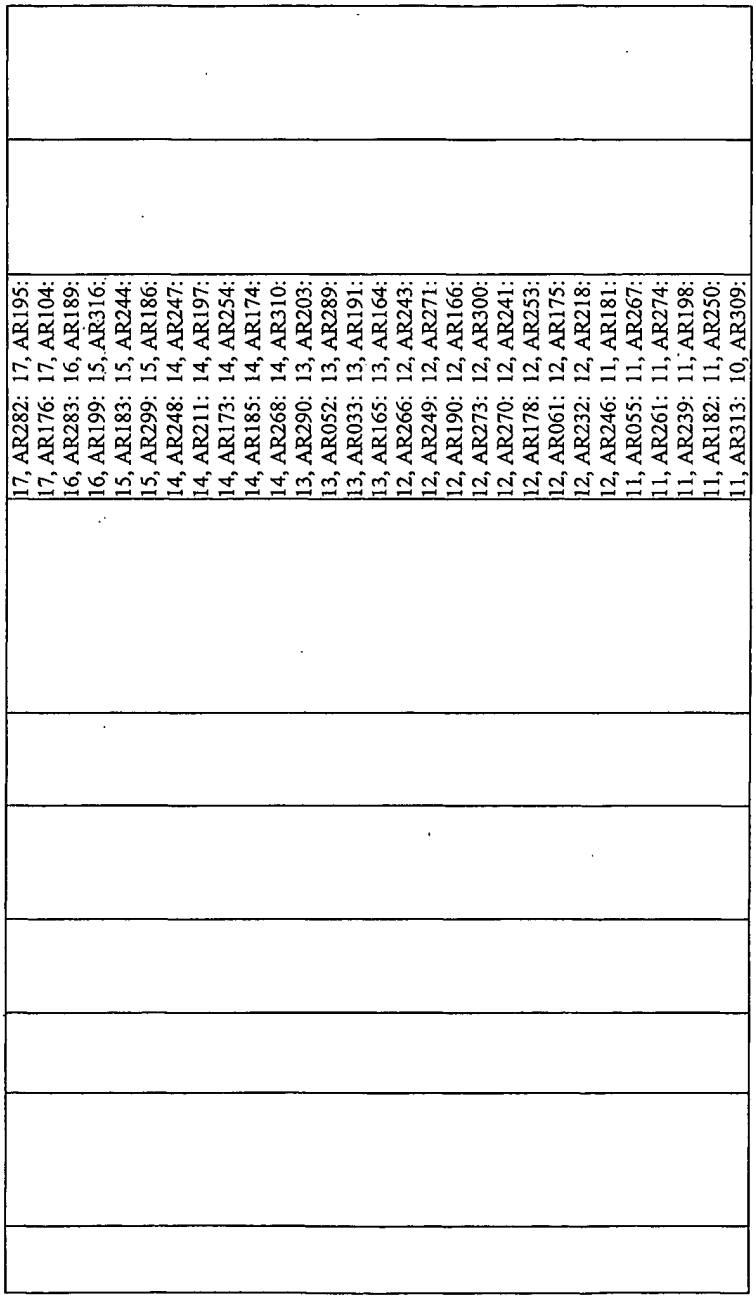
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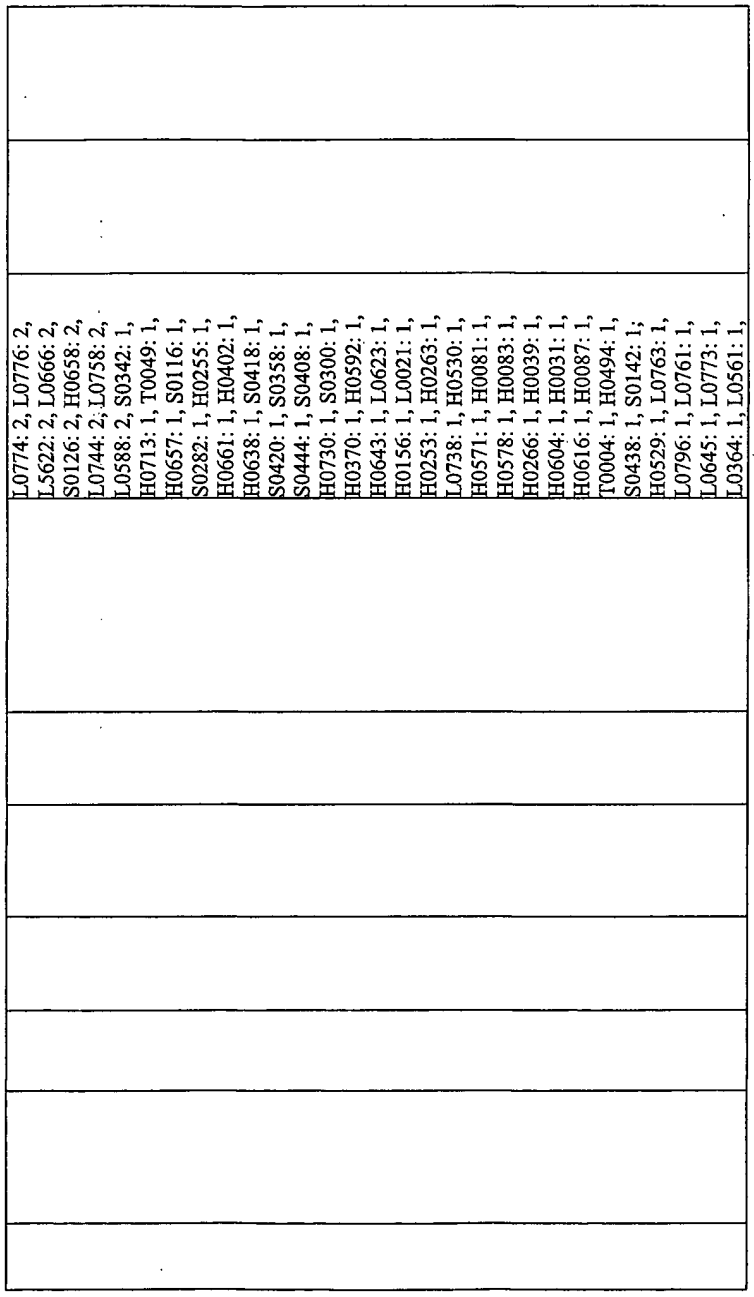
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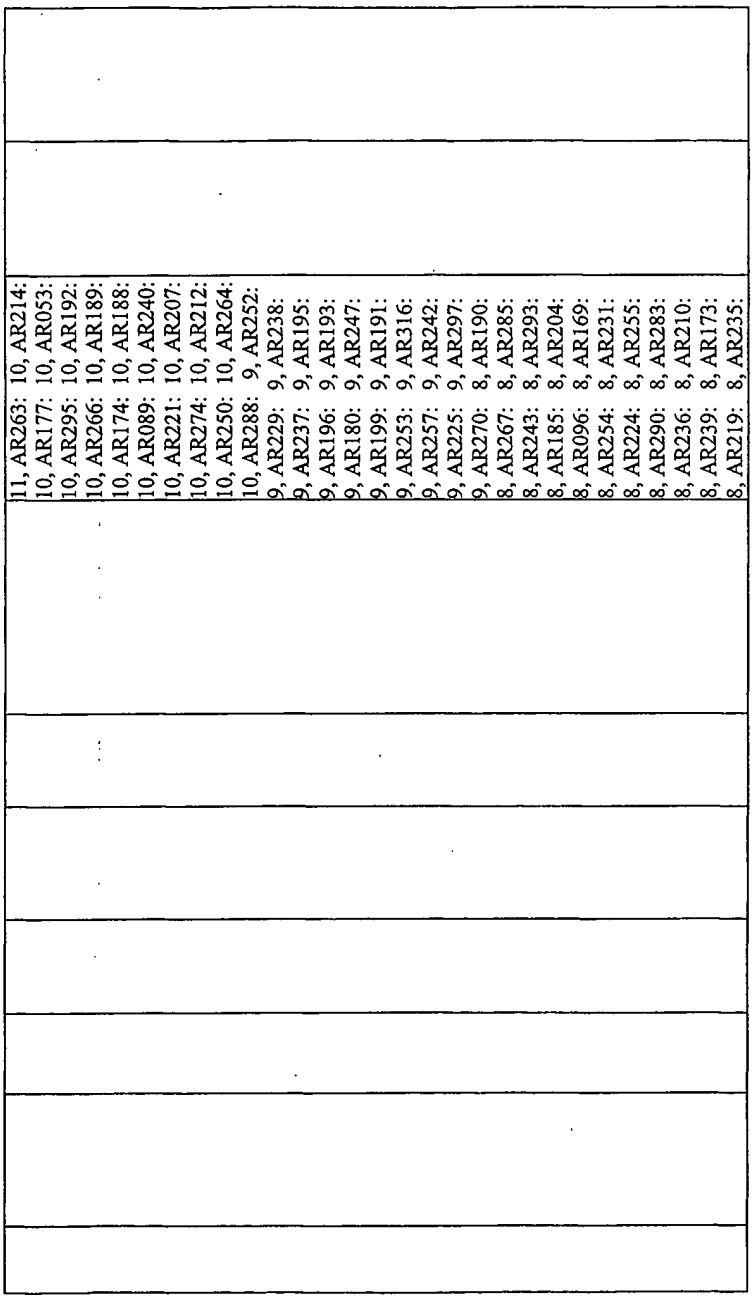

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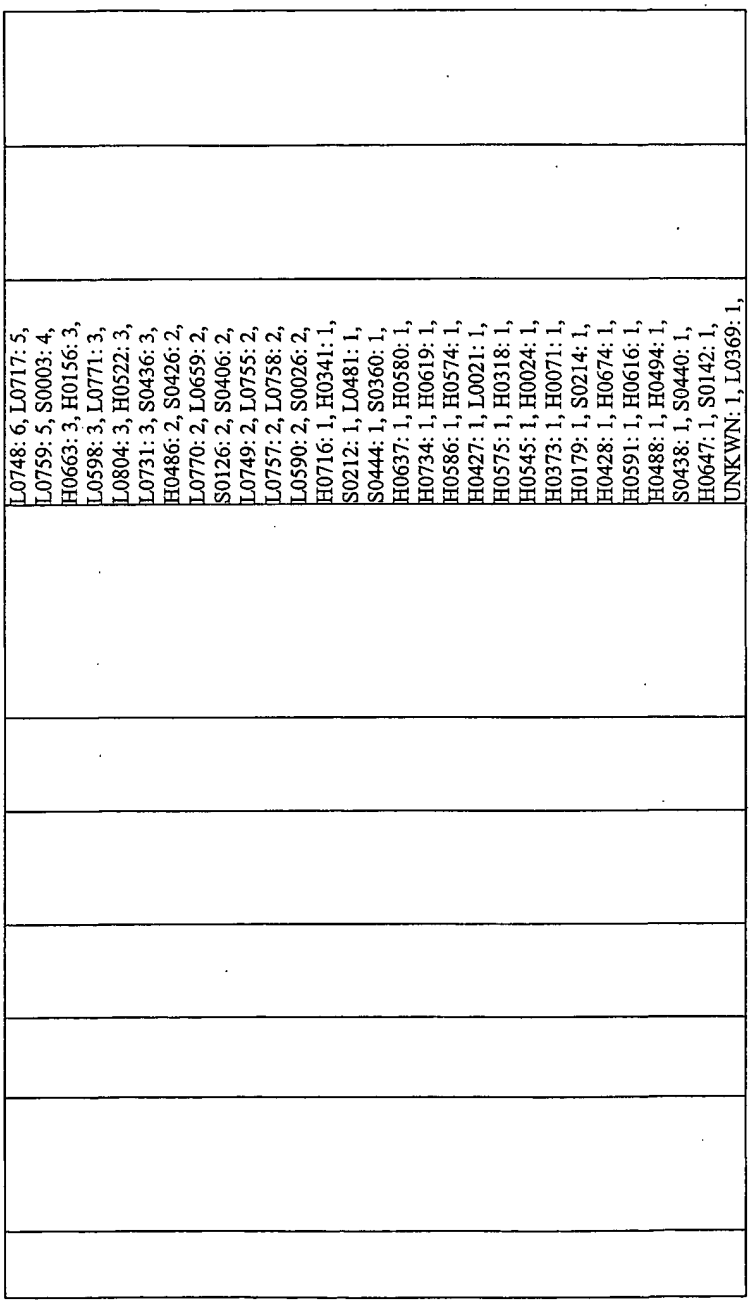
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18	HRACJ35	730504	28	99 - 1517	121	Arg-31 to Lys-37, Lys-58 to Glu-65, Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.	AR222: 51, AR224: 51, AR221: 28, AR223: 24, AR225: 20, AR172: 14, AR171: 9, AR170: 9, AR182: 9, AR215: 9, AR214: 9, AR183: 8, AR216: 8, AR169: 8, AR168: 7, AR268: 7, AR217: 7, AR180:			148900, 216550	

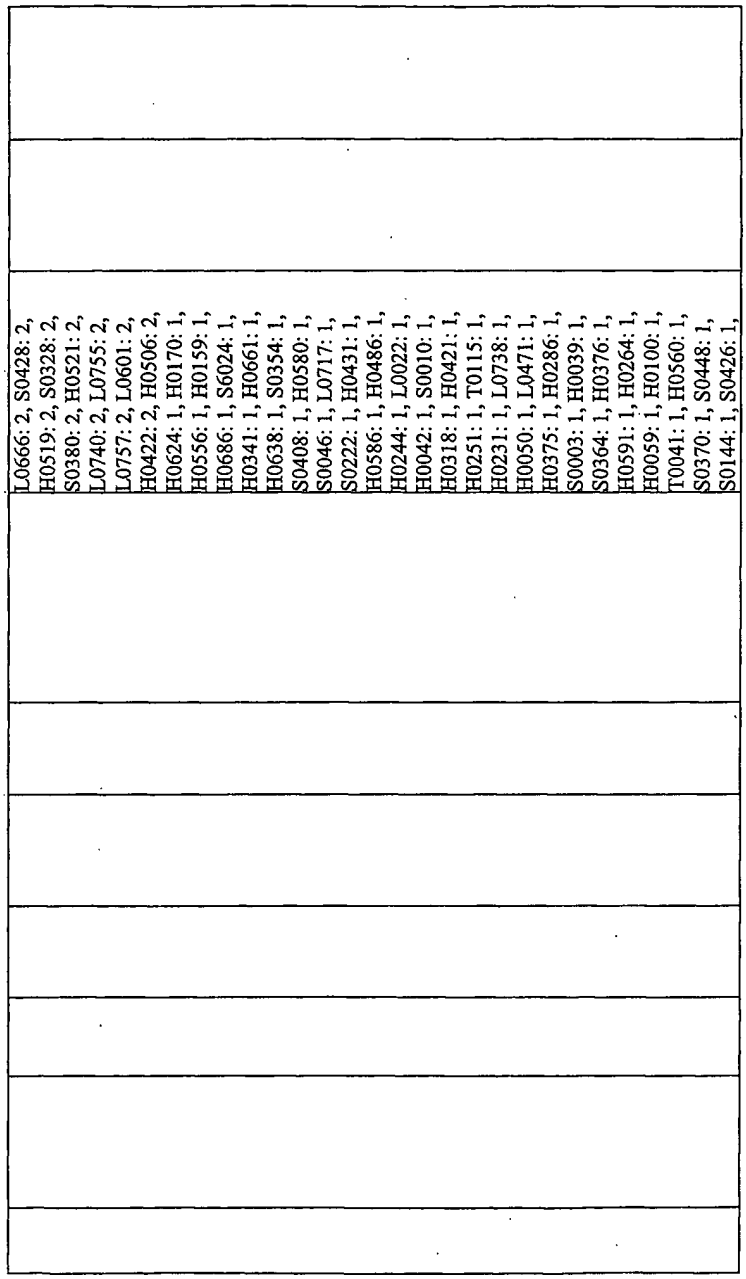
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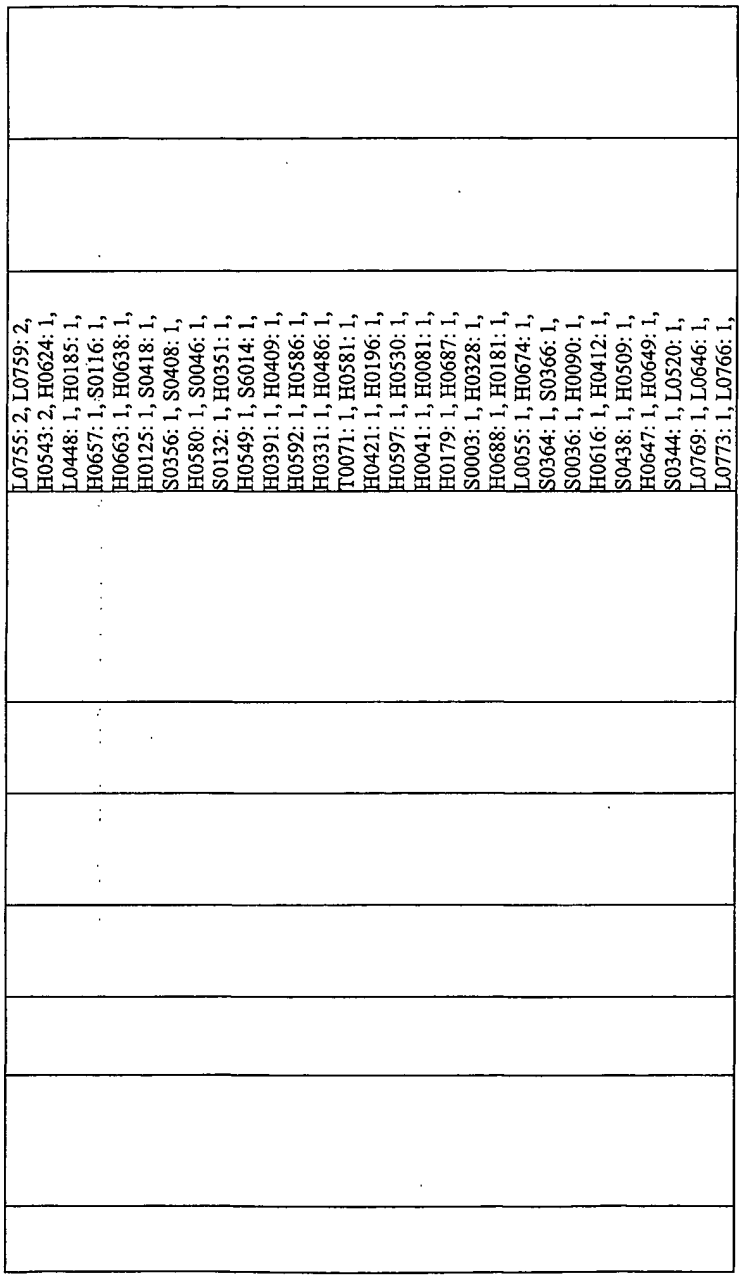
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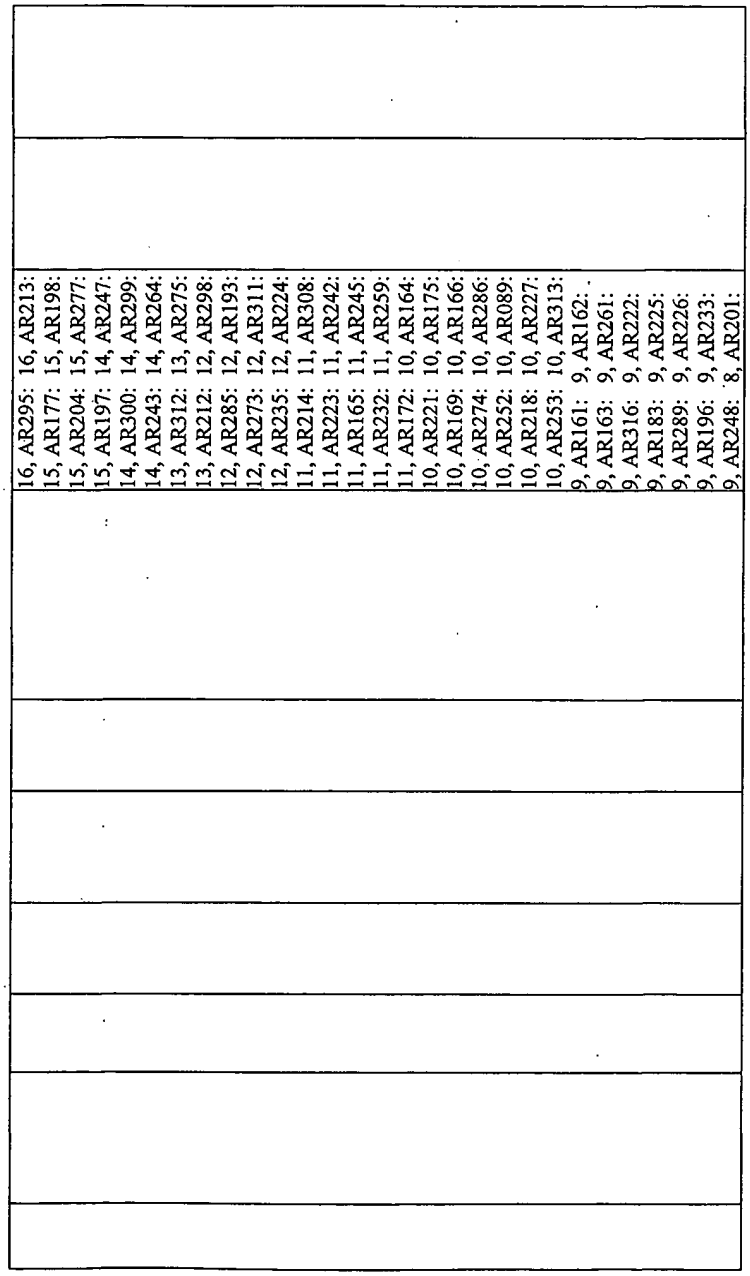

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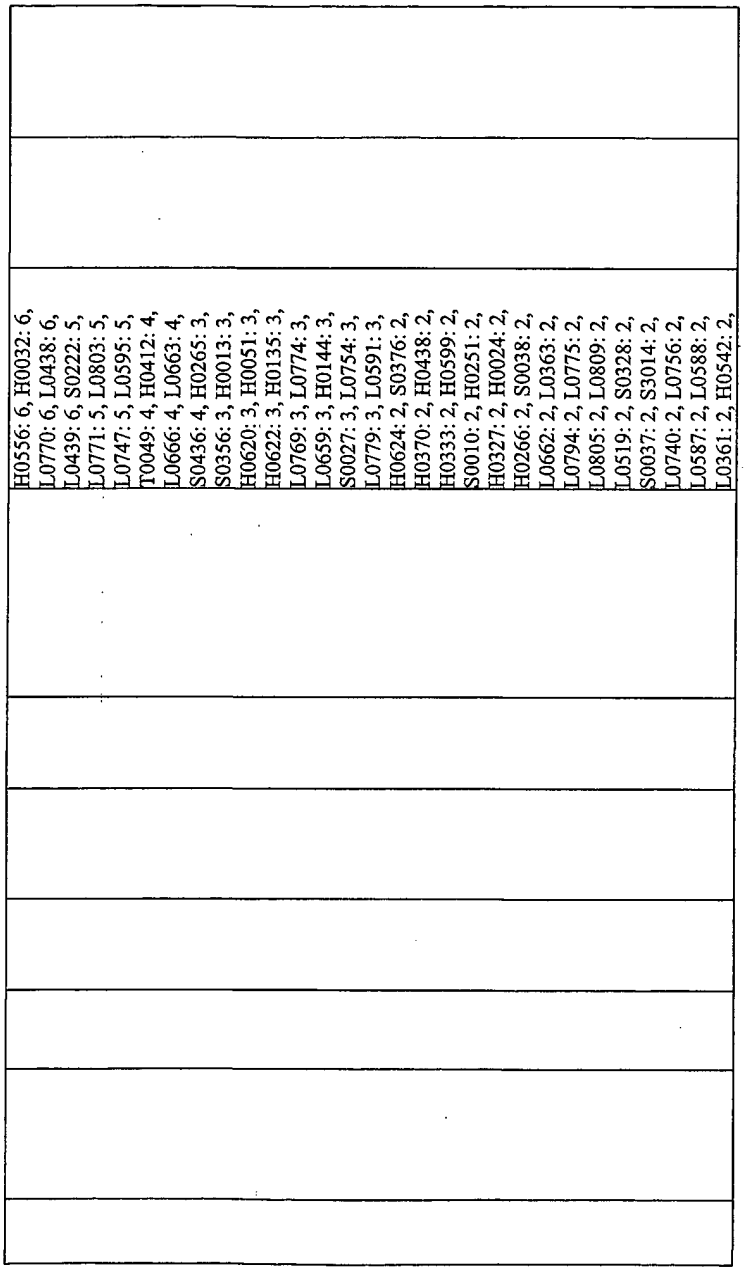
26	HCEJG71	715592	36	28 - 1368	129	Pro-122 to Lys-127, Gln-138 to Asn-146, Cys-280 to Lys-287, Asp-306 to Gly-311, Asp-321 to Thr-326, Gly-337 to Pro-345, Thr-354 to Gln-359, Asn-451 to Arg-456.	AR060: 198, AR185: 189, AR299: 177, AR104: 153, AR283: 143, AR240: 119, AR282: 116, AR316: 113, AR277: 101, AR089: 100, AR096: 75, AR313: 54 H0038: 8, H0618: 7, L0747: 6, L0758: 5, H0135: 4, H0616: 4, H0024: 3, H0547: 3, S0406: 3, L0439: 3, L0777: 3, L0759: 3, S0420: 2, H0208: 2, H0370: 2, H0014: 2, S0344: 2, L0788: 2, L0666: 2, S0374: 2, L0438: 2, L0751: 2, S0436: 2, S0040: 1, S0342: 1, H0716: 1,	7q11.23	116860, 129900, 233700, 600079

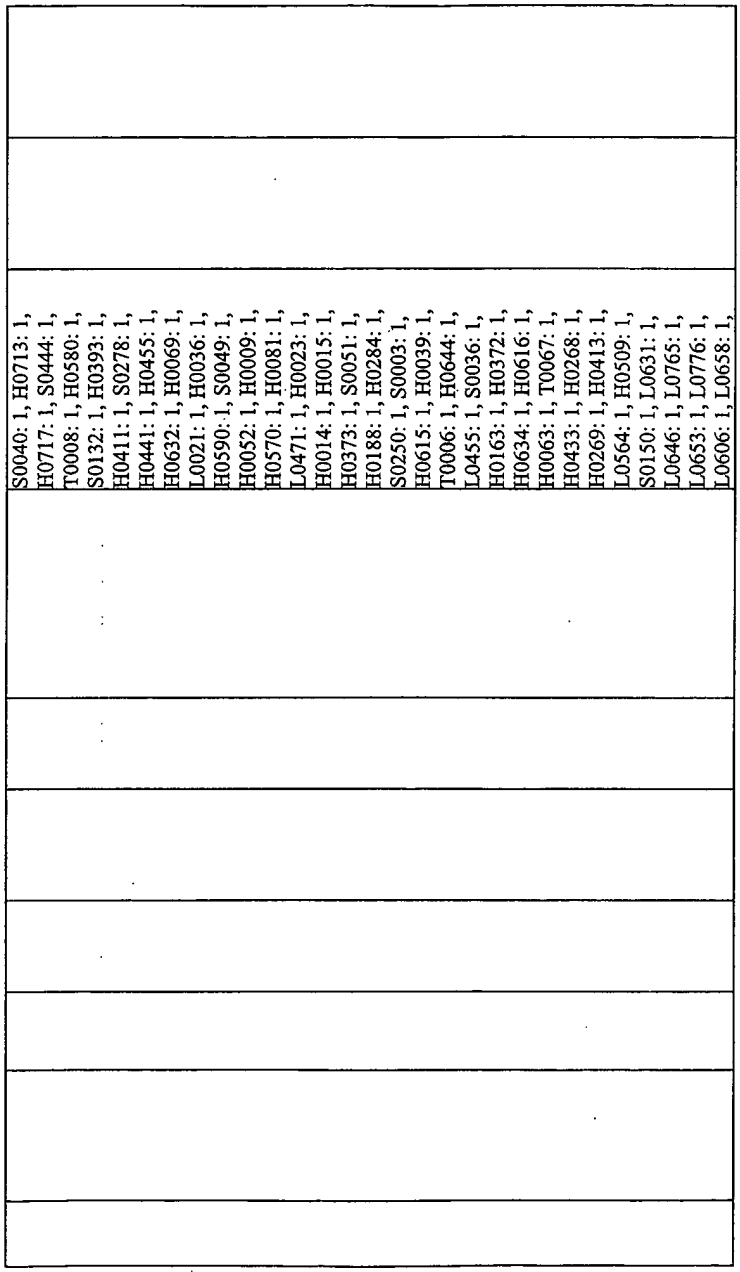
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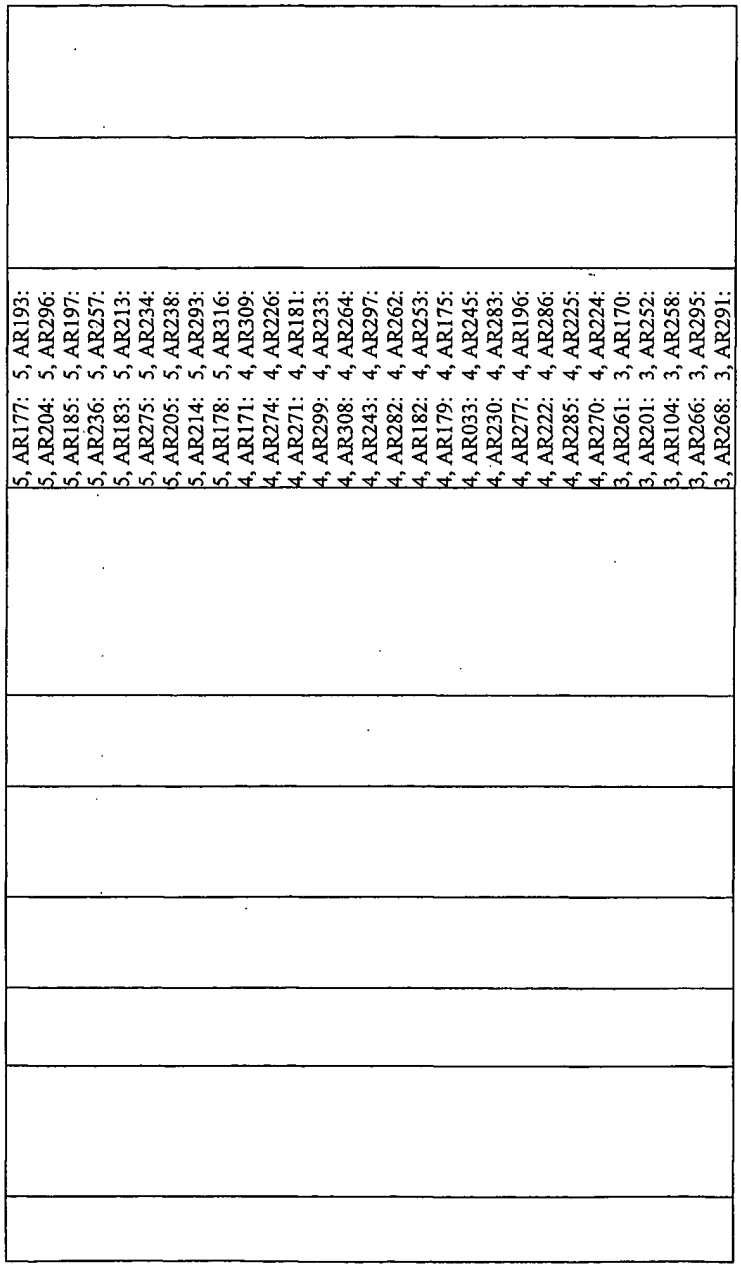
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28	HISAQ04	589960	38	61 - 294	131	Thr-27 to Ser-33.	AR313: 12, AR089: 10, AR165: 10, AR162: 10, AR164: 9, AR242: 9, AR161: 9, AR192: 9, AR166: 9, AR163: 9, AR207: 8, AR173: 8, AR300: 7, AR198: 7, AR263: 6, AR180: 6, AR195: 6, AR240: 6, AR247: 6, AR169: 6, AR096: 6, AR053: 6, AR039: 5, AR212: 5, AR229: 5, AR060: 5, AR174: 5, AR312:		


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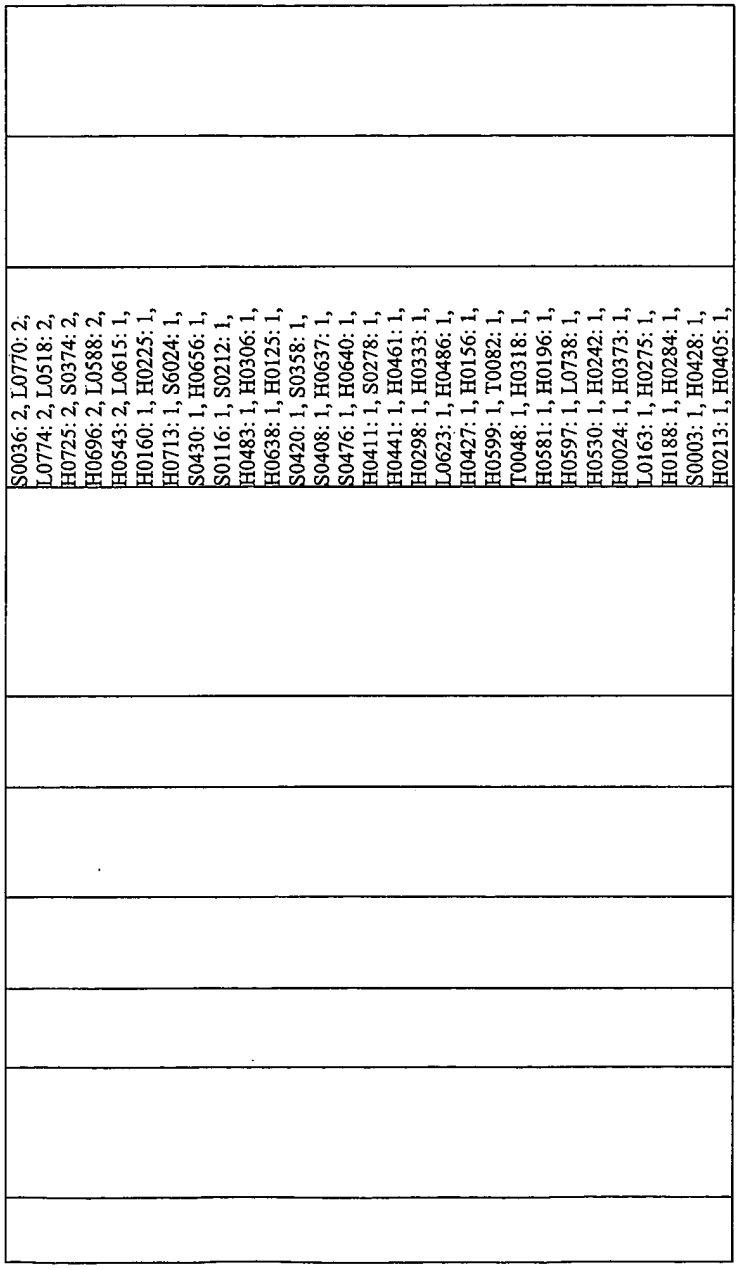
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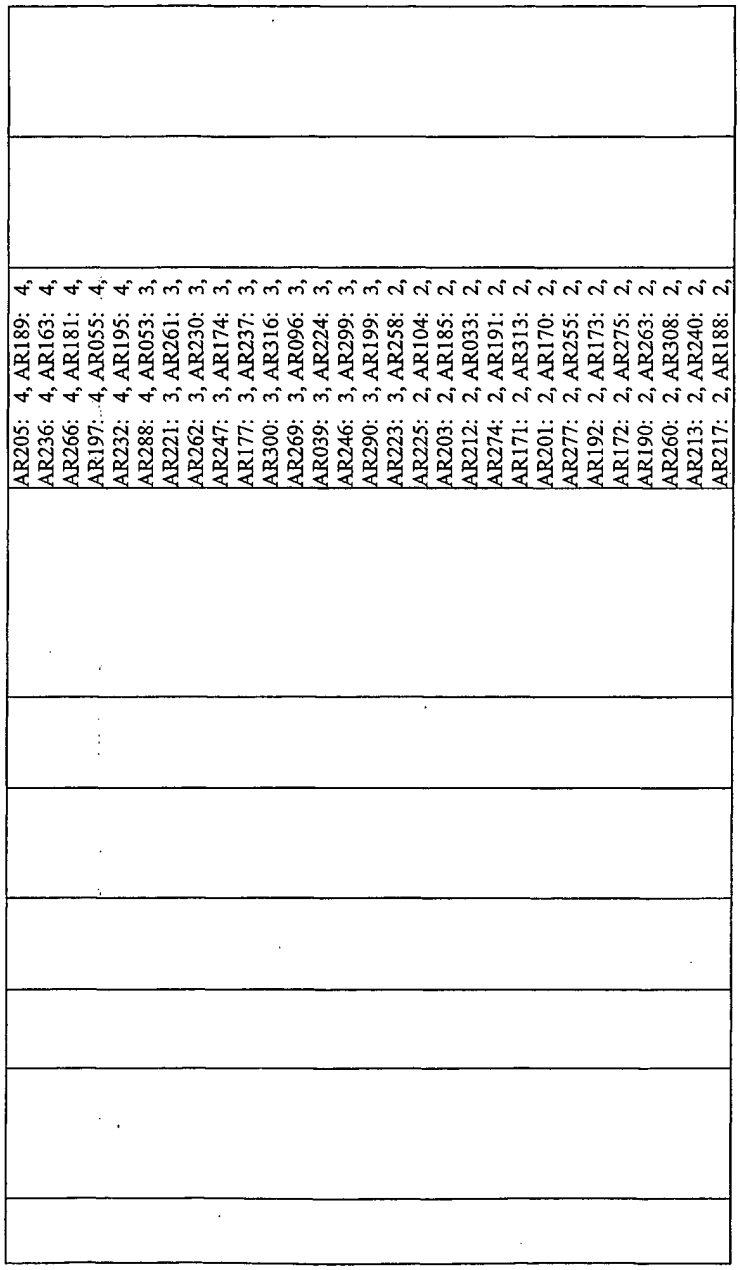

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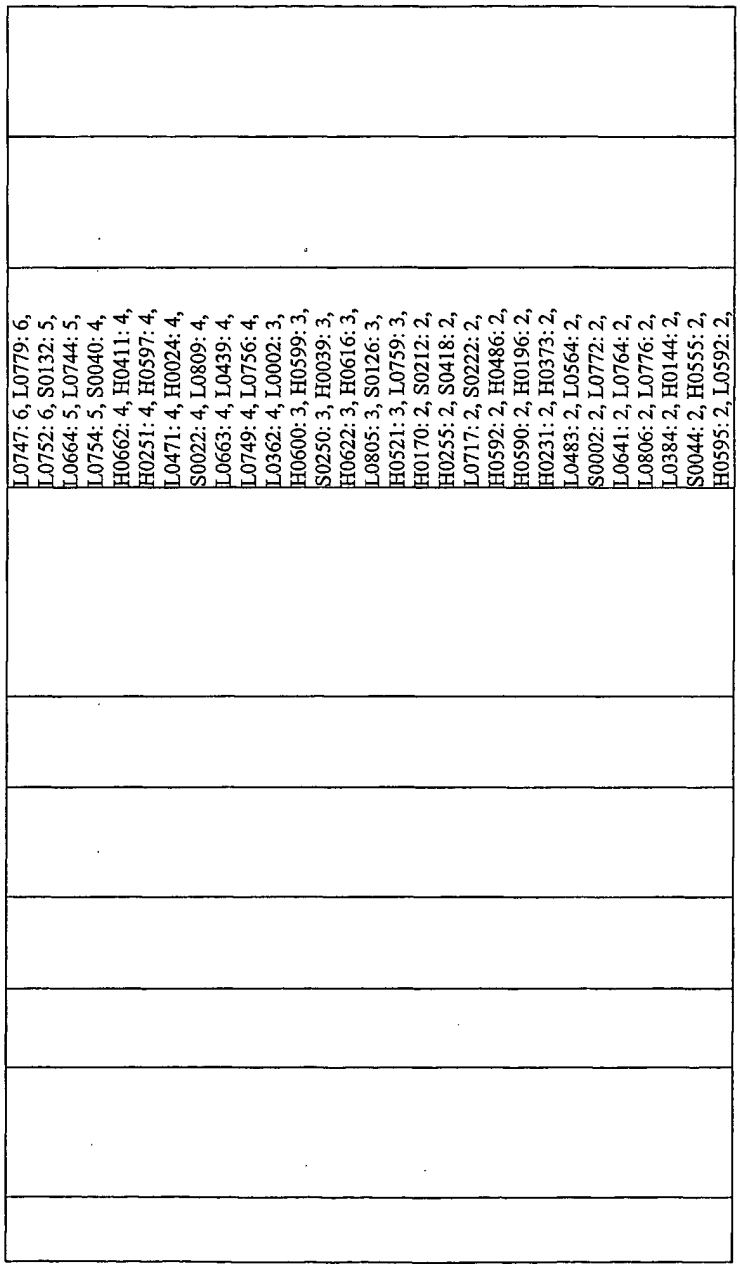
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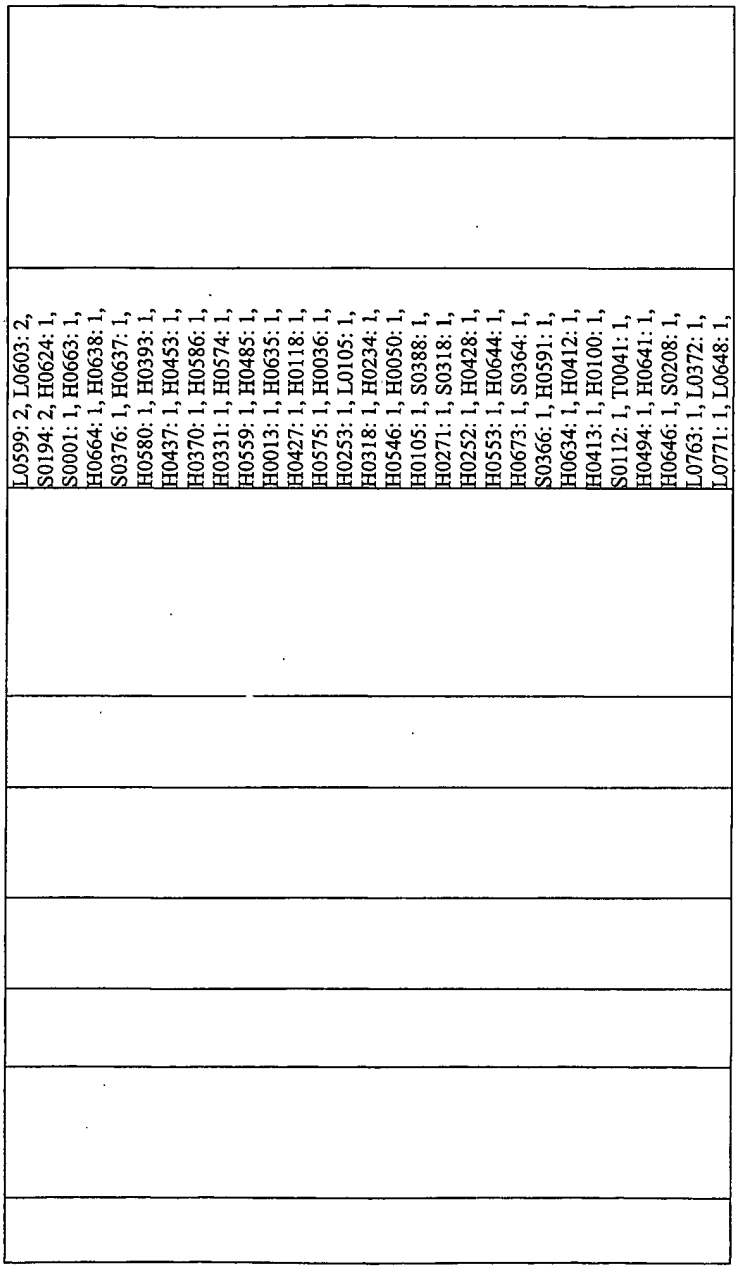
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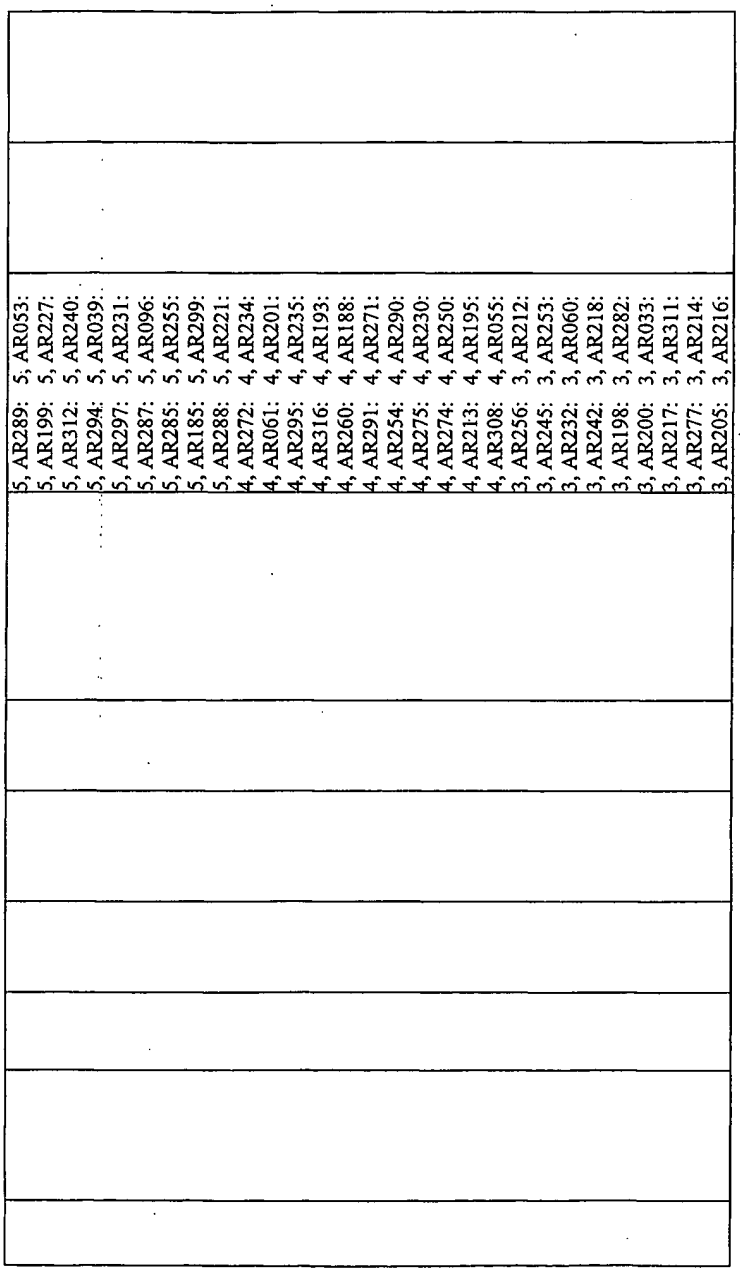

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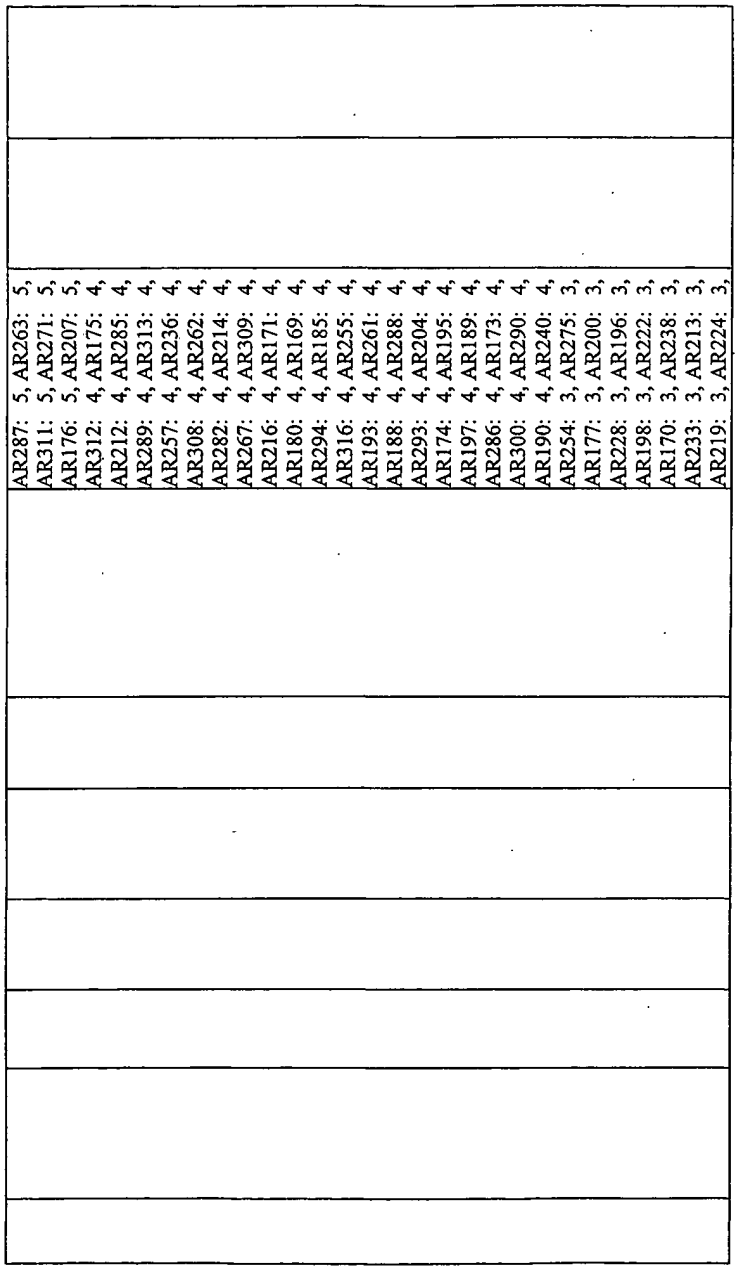
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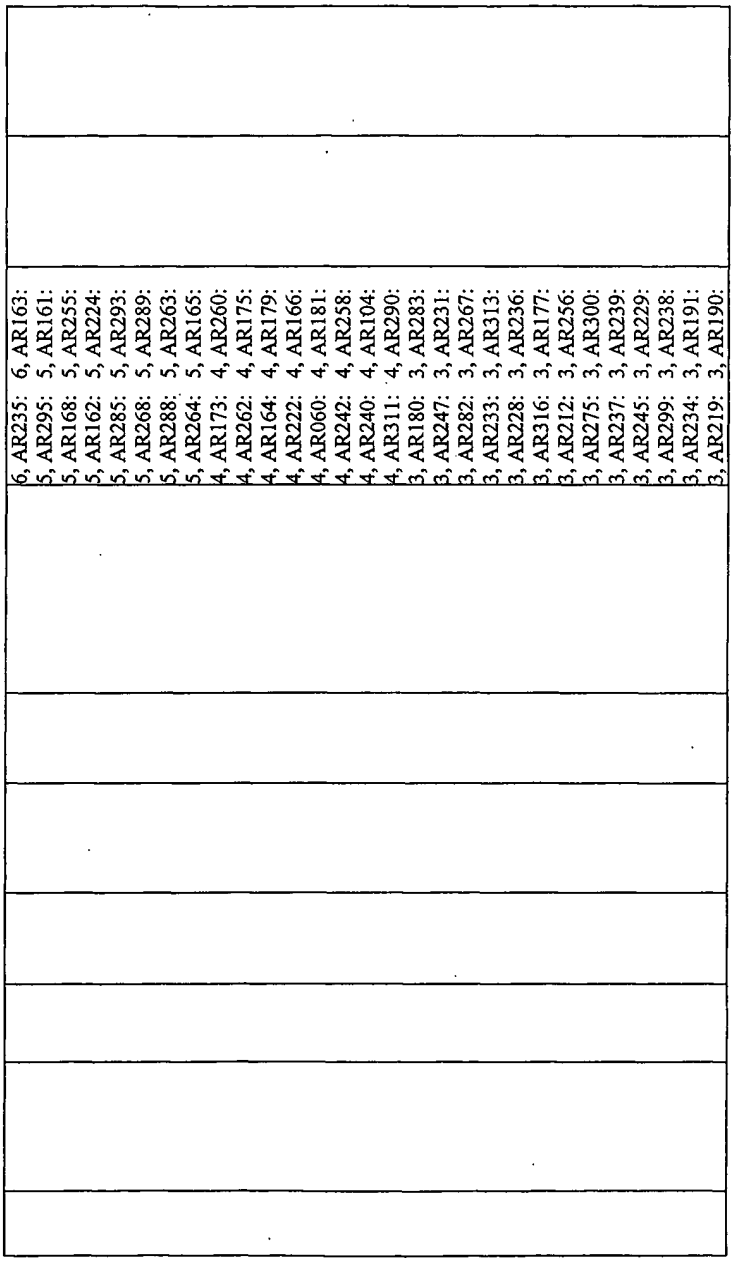
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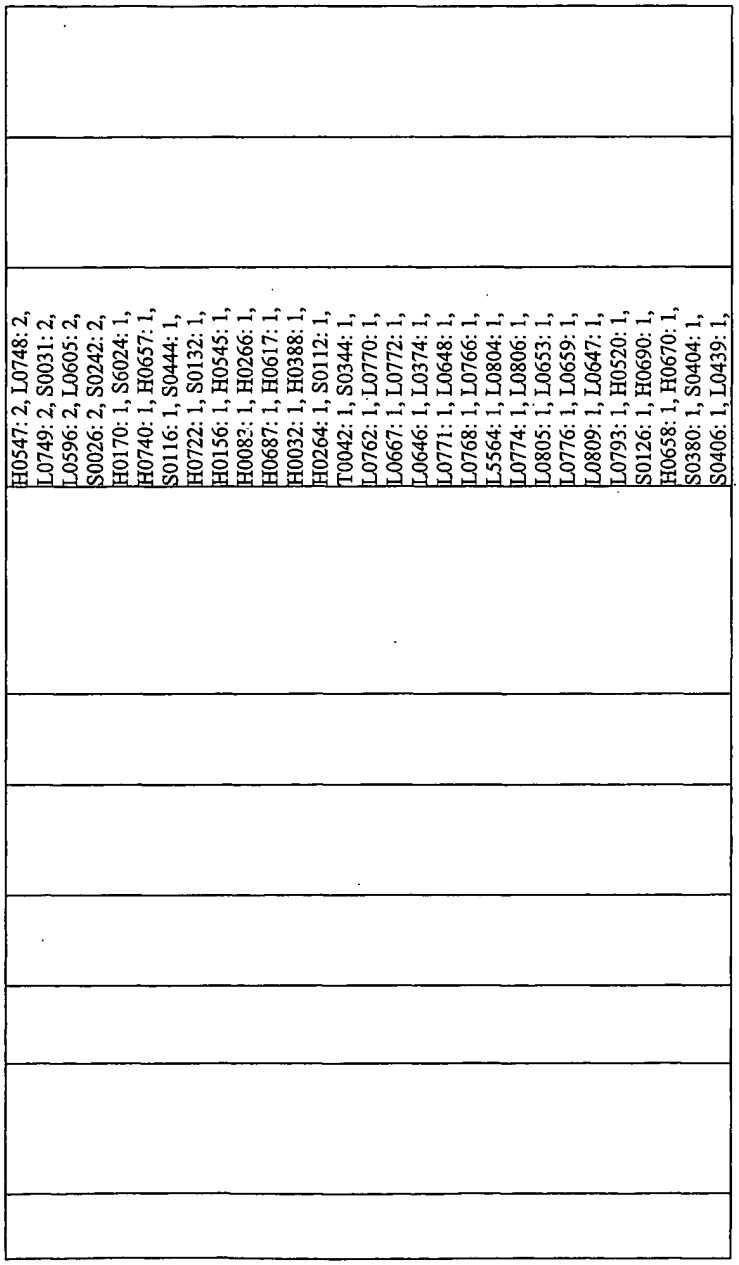
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47	HKAEA19	721489	57	83 - 352	150		H0711: 1, H0658: 1, H0670: 1, S0152: 1, S0350: 1, H0696: 1, H0704: 1, L0749: 1, L0777: 1, L0731: 1, L0757: 1, L0588: 1, S0276: 1 and H0543: 1.	AR170: 3, AR197: 3, AR275: 2, AR205: 2, AR168: 2, AR250: 2, AR264: 2, AR217: 2, AR175: 2, AR313: 2, AR214: 1, AR213: 1, AR172: 1, AR282: 1, AR161: 1, AR162: 1, AR247: 1, AR216: 1, AR096: 1, AR295: 1, AR194: 1, AR271: 1, AR193: 1, AR289: 1, AR224: 1, AR257: 1, AR225: 1, AR248: 1, AR178: 1 S0358: 6, L0777: 6, H0494: 5, L0664: 4, L0747: 4, L0775: 3, L0789: 3, L0663: 3, L0665: 3, L0438: 3, L0741: 3, S0360: 2, H0051: 2, L0662: 2,	12q11-q12	600194, 600231, 601284, 601769, 601769

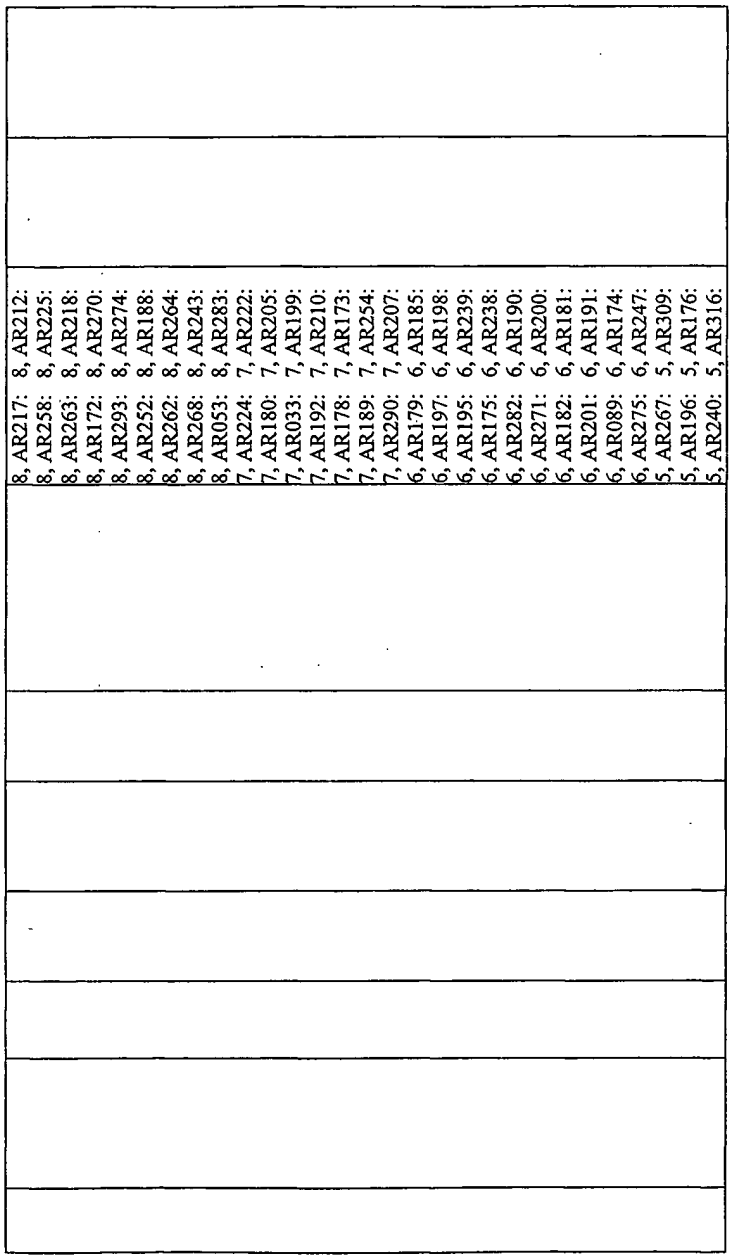

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49	HLDBS43	722228	59	73 - 1245	152	Pro-85 to Ser-94, Pro-127 to Thr-136, Glu-154 to Glu-160, Phe-240 to Ser-250, Leu-255 to Leu-265, Leu-341 to Lys-351, Thr-372 to Gly-384.	L0647: 1, L0787: 1, H0684: 1, H0672: 1, L0749: 1, L0753: 1, L0759: 1, S0260: 1, S0434: 1 and S0436: 1.	AR291: 18, AR169: 15, AR171: 15, AR266: 14, AR168: 14, AR289: 13, AR297: 13, AR257: 13, AR170: 12, AR285: 12, AR214: 12, AR287: 12, AR260: 12, AR255: 11, AR216: 11, AR165: 11, AR296: 11, AR164: 11, AR183: 11, AR223: 11, AR213: 10, AR166: 10, AR215: 10, AR272: 10, AR311: 10, AR253: 10, AR193: 10, AR294: 10, AR261: 10, AR246: 10, AR295: 10, AR219: 9, AR288: 9, AR162: 9, AR161: 9, AR269: 9, AR308: 9, AR236: 9, AR231: 9, AR163: 9, AR313: 9, AR039: 9, AR256: 9, AR235: 9, AR250: 8, AR245: 8, AR312: 8, AR286:	12	

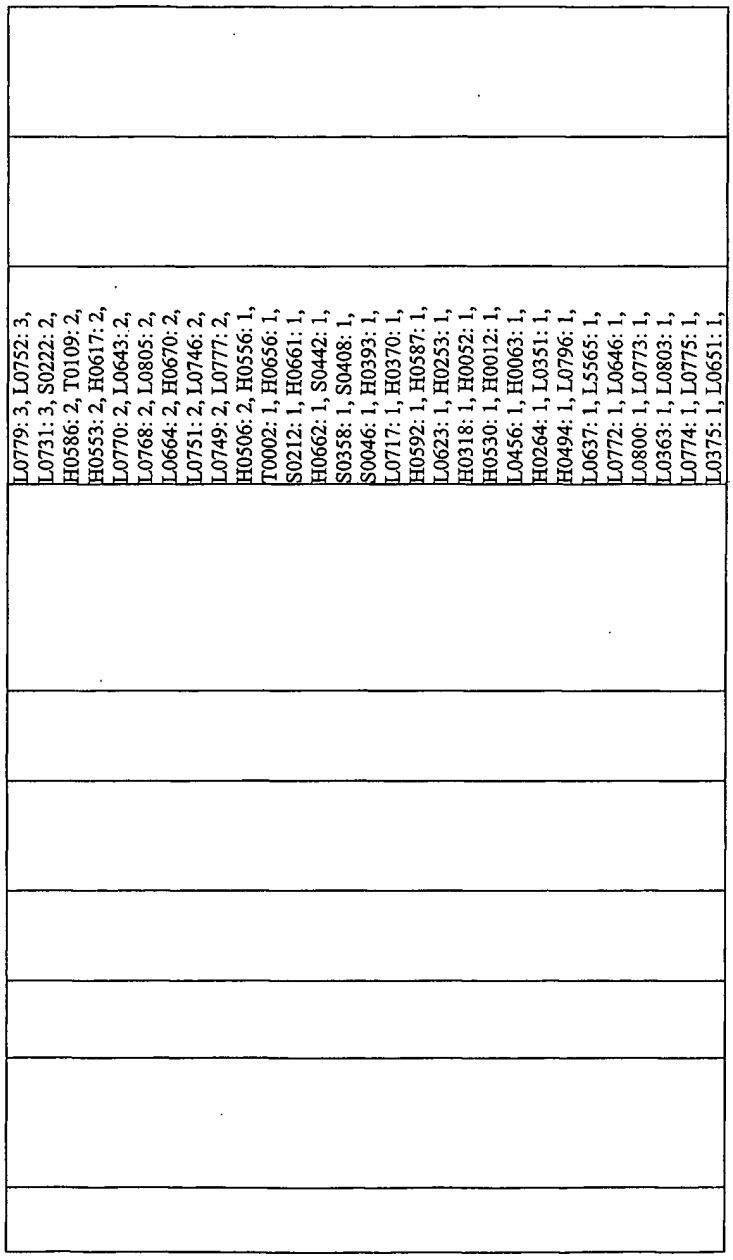

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52	HMEJE05	722231	62	25 - 1203	155	Ala-21 to Lys-31, Arg-41 to Cys-56, Thr-92 to Cys-102, Arg-132 to Val-137, Lys-152 to Ile-159, Pro-199 to Ser-205, Arg-210 to Asp-219, Ser-225 to Lys-230, Tyr-236 to Ala-241,	AR060: 4, AR282: 4, 3 AR269: 3, AR283: 3, AR178: 3, AR180: 3, AR240: 3, AR089: 3, AR254: 3, AR215: 2, AR173: 2, AR252: 2, AR272: 2, AR217: 2, AR277: 2, AR313: 2, AR316: 2, AR268: 2,		

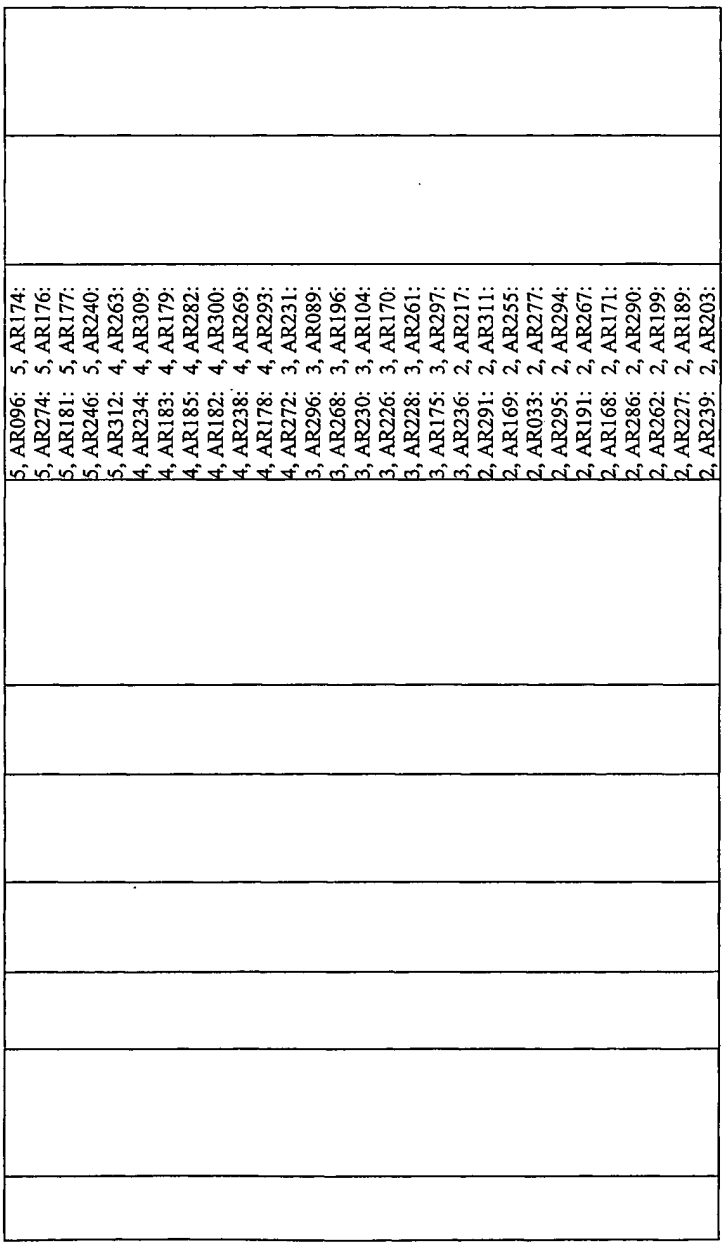
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53	HNGIX55	695749	63	121 - 345	156	Gly-63 to Ser-72.	H0521: 1, S0028: 1, L0779: 1, L0759: 1 and S0424: 1.	AR223: 5, AR282: 4, AR215: 4, AR168: 4, AR291: 4, AR266: 4, AR214: 4, AR253: 3, AR269: 3, AR308: 3, AR217: 3, AR235: 3, AR270: 3, AR225: 3, AR289: 3, AR261: 3, AR171: 3, AR183: 3, AR165: 3, AR222: 3, AR164: 3, AR166: 2, AR216: 2, AR196: 2, AR312: 2, AR268: 2, AR169: 2, AR287: 2, AR176: 2, AR293: 2, AR188: 2, AR290: 2, AR257: 2, AR267: 2, AR295: 2, AR053: 2, AR204: 2, AR182: 2, AR255: 2, AR228: 2, AR207: 2, AR286: 2, AR285: 2, AR232: 2, AR210: 2, AR175: 2, AR174: 2, AR236: 2, AR229: 2, AR271: 2, AR258: 2, AR313: 1,		

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54	HNHEX30	634848	64	138 - 383	157	Ile-28 to Trp-37, Ser-68 to Lys-81.	AR199: 16, AR210: 16, AR272: 14, AR309: 13, AR195: 13, AR196: 13, AR197: 12, AR235: 12, AR245: 12, AR261: 11, AR308: 11, AR264: 10, AR253: 10, AR211: 10, AR162: 9, AR282: 9, AR218: 9, AR033: 9, AR207: 9, AR161: 9, AR188: 9, AR295: 8, AR165: 8, AR104: 8, AR163: 8, AR263: 8, AR164: 8, AR191: 8, AR166: 8, AR192: 8, AR198: 8, AR189: 8, AR089: 7, AR200:		

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57	HRACD80	882163	67	191 - 1915	160	Lys-32 to Ser-37, His-89 to Gly-94, Asn-124 to Gln-130, Ala-163 to Val-168, Cys-196 to Arg-201, Gln-244 to Gln-264, His-288 to Tyr-294, Leu-314 to Gln-319, Ala-392 to Ser-399, Pro-412 to Asp-419, Ala-452 to Pro-460, Arg-466 to Thr-473.	AR290: 353, AR268: 210, AR241: 164, AR202: 124, AR313: 113, AR198: 111, AR242: 111, AR267: 111, AR243: 105, AR096: 96, AR203: 94, AR246: 93, AR213: 91, AR270: 88, AR201: 80, AR200: 78, AR300: 77, AR245: 69, AR183: 64, AR053: 61, AR173: 55, AR234: 55, AR244: 54, AR189: 43, AR240: 38, AR188: 38, AR193: 32, AR289: 31, AR231: 30, AR194: 29, AR207: 28, AR205: 27, AR206: 26, AR055: 26, AR228: 25, AR266: 25, AR164: 24, AR165: 24, AR175: 22, AR166: 22, AR273: 21, AR192: 20, AR299: 20, AR163: 20, AR039: 20, AR161: 19, AR162:		

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58	HSLCX03	889145	68	677 - 2605	161	Gly-2 to Pro-8, Ser-82 to His-92, Tyr-107 to Asp-117, Arg-162 to Pro-169, Ser-224 to Thr-229, Leu-310 to His-315, Ser-333 to Glu-338, Glu-381 to Ser-388, Gln-428 to Ala-433, Met-446 to Thr-455, Ser-548 to Ser-554, Gly-613 to Asp-618, Ser-627 to Gln-633.	AR241: 5, AR184: 5, AR202: 5, AR273: 4, AR206: 4, AR284: 4, AR225: 3, AR263: 3, AR235: 3, AR052: 3, AR186: 3, AR251: 3, AR282: 3, AR053: 3, AR275: 3, AR309: 3, AR183: 3, AR245: 2, AR312: 2, AR298: 2, AR055: 2, AR246: 2, AR292: 2, AR205: 2, AR264: 2, AR291: 2, AR270: 2, AR221: 2, AR267: 2, AR175: 2, AR061: 2, AR269: 2, AR201: 2, AR182: 2, AR180: 2, AR310: 2, AR224: 2, AR313: 2, AR033: 2, AR289: 2, AR257: 2, AR247: 2, AR161: 2, AR285: 2, AR290: 2, AR039: 2, AR162: 2, AR060: 2, AR299: 2, AR268: 2, AR168: 1, AR164: 1, AR096: 1, AR163: 1,		

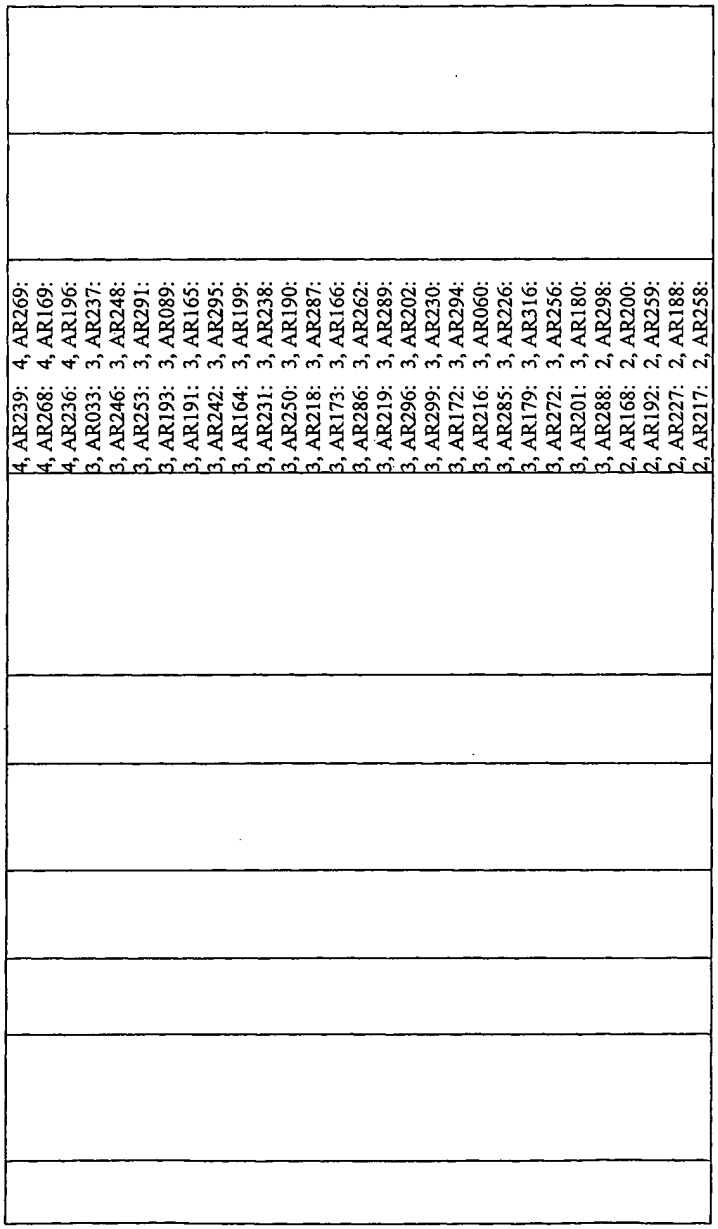
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59	HT5GJ57	740767	69	122 - 694	162	Ser-29 to Thr-57, Pro-74 to Lys-79, Pro-85 to Glu-107, Tyr-118 to Tyr-136, Gln-144 to Gln-152, Ala-182 to Glu-188.	AR213: 5, AR264: 4, AR224: 4, AR254: 4, AR253: 4, AR207: 4, AR053: 3, AR197: 3, AR161: 3, AR162: 3, AR163: 3, AR250: 3, AR221: 3, AR171: 3, AR311: 3, AR212: 3, AR165: 3, AR215: 3, AR282: 3, AR217: 2, AR309: 2, AR263: 2, AR193: 2, AR195: 2, AR089: 2, AR168: 2, AR166: 2, AR164: 2, AR312: 2, AR308: 2, AR223: 2, AR183: 2, AR267: 2, AR169: 2,	7q11.23	116860, 129900, 233700, 600079

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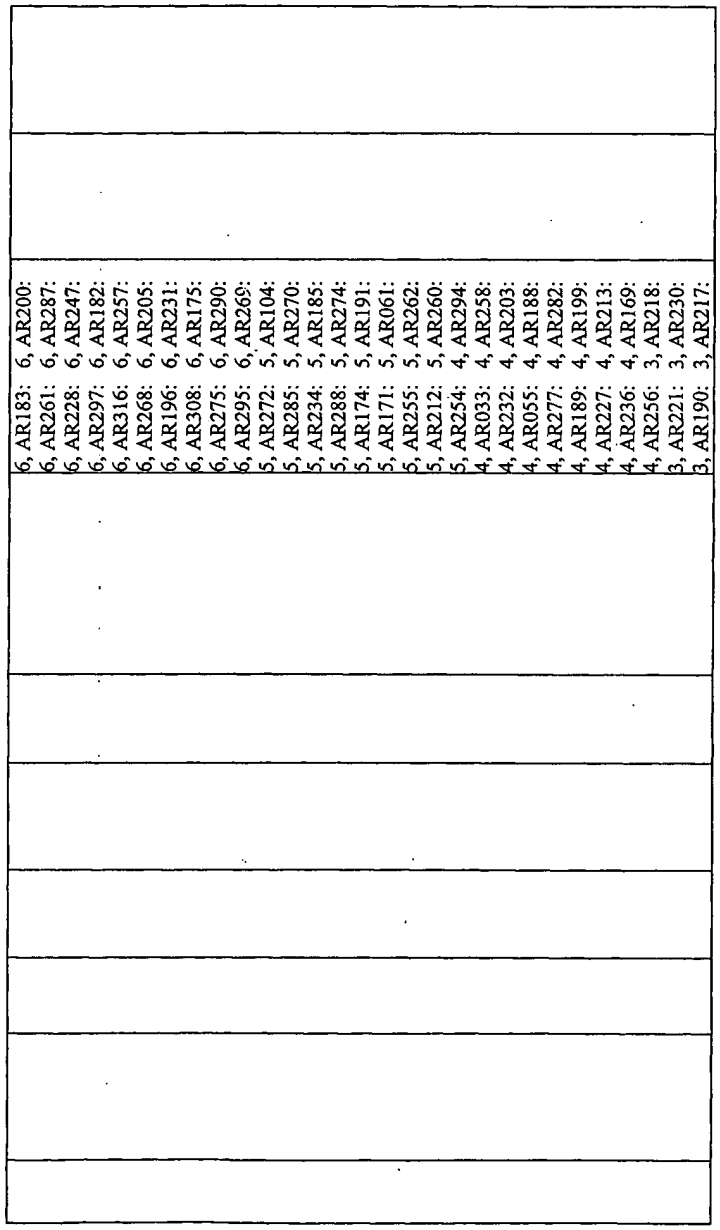
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61	HTEKE40	740768	71	173 - 526	164			
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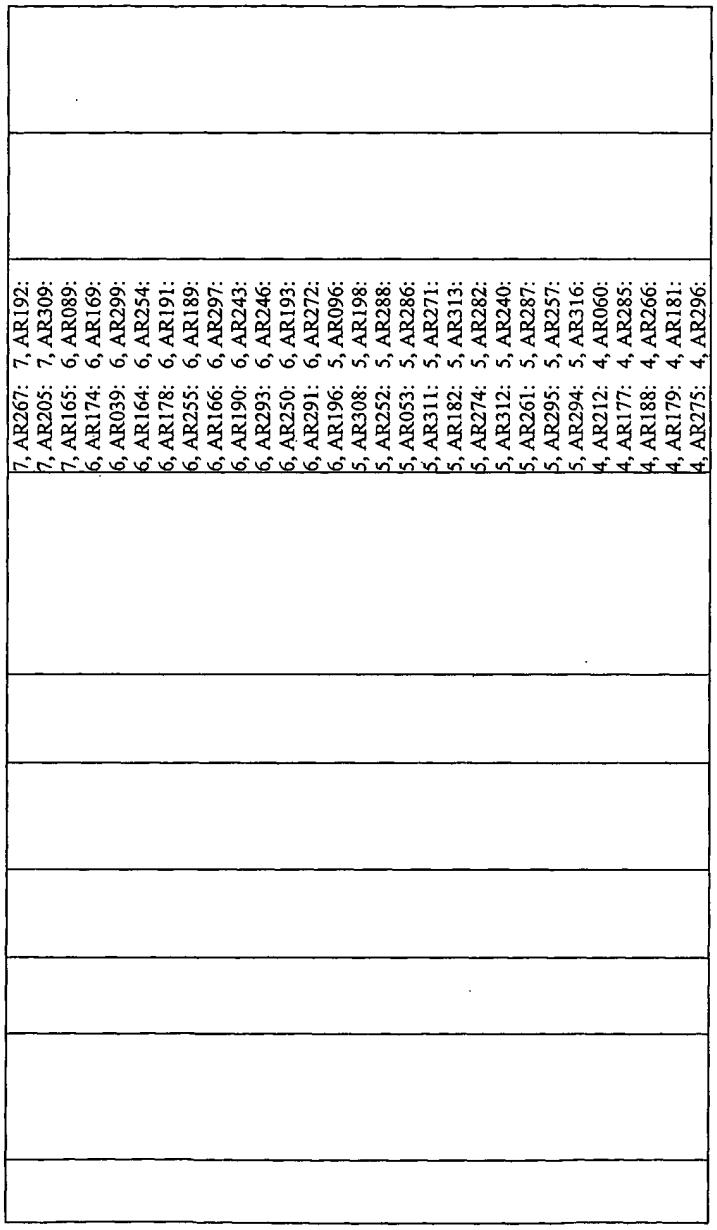

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62	HTOBX69	722255	72	28 - 156	165		
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64	H2CBG48	745365	74	125 - 262	167	AR223: 3, AR171: 3, AR282: 3, AR164: 3, AR166: 3, AR215: 3, AR246: 2, AR176: 2, AR195: 2, AR216: 2, AR165: 2, AR261: 2,		

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65	H2CBU83	884134	75	157 - 777	168	Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168.	AR182: 8, AR314: 7, AR271: 7, AR280: 6, AR315: 6, AR216: 6, AR052: 6, AR224: 6, AR225: 5, AR164: 5, AR215: 5, AR270: 5, AR165: 5, AR162: 5, AR310: 5, AR245: 5, AR166: 5, AR161: 5, AR169: 5, AR223: 5, AR266: 5, AR172: 5, AR192: 5, AR163: 4, AR282: 4, AR193: 4, AR207: 4, AR176: 4, AR269: 4, AR175: 4, AR226: 4, AR243: 4, AR217: 4, AR273: 4, AR168: 4, AR204: 4, AR299: 4, AR291: 4, AR265: 4, AR183: 4, AR274: 4, AR214: 4, AR205: 4, AR206: 4, AR194: 4, AR060: 4, AR272: 4, AR238: 4, AR186: 4, AR222: 4, AR089: 4, AR053: 4,		102772, 106210, 106210, 106210, 106210, 107271, 114550, 115500, 136530, 151390, 179615, 179615, 179616, 180385, 194070, 194070, 194070, 245349, 602092

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66	HAPNY94	699770	76	94 - 246	169	Ser-30 to Trp-37.	AR253: 10, AR309: 9, AR161: 6, AR162: 6, AR163: 6, AR263: 6, AR266: 5, AR264: 5,	6p25	134570, 601090, 602028

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AR283: 1, AR060: 1,
AR211: 1, AR219: 1
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L0803: 3, H0547: 3,
L0779: 3, H0422: 3,
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H0484: 2, S0410: 2,

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67	HBJHZ58	745372	77	102 - 230	170	Asp-33 to Lys-42.	AR245: 7, AR161: 5, AR162: 5, AR163: 5, AR309: 5, AR197: 5, AR264: 4, AR225: 4, AR193: 4, AR271: 3, AR039: 3, AR250: 3, AR176: 3, AR246: 3, AR181: 3, AR198: 3, AR169: 2, AR242: 2, AR165: 2, AR195: 2, AR096: 2, AR269: 2, AR166: 2, AR201: 2, AR274: 2, AR272: 2, AR233: 2, AR089: 2, AR205: 2, AR267: 2, AR196: 2, AR270: 2, AR312: 2, AR228: 2, AR055: 1, AR174: 1, AR226: 1, AR296: 1, AR262: 1, AR164: 1, AR313: 1, AR168: 1, AR178: 1, AR293: 1, AR277: 1, AR185: 1, AR311: 1, AR239: 1, AR288: 1, AR282: 1, AR182: 1, AR216: 1,		

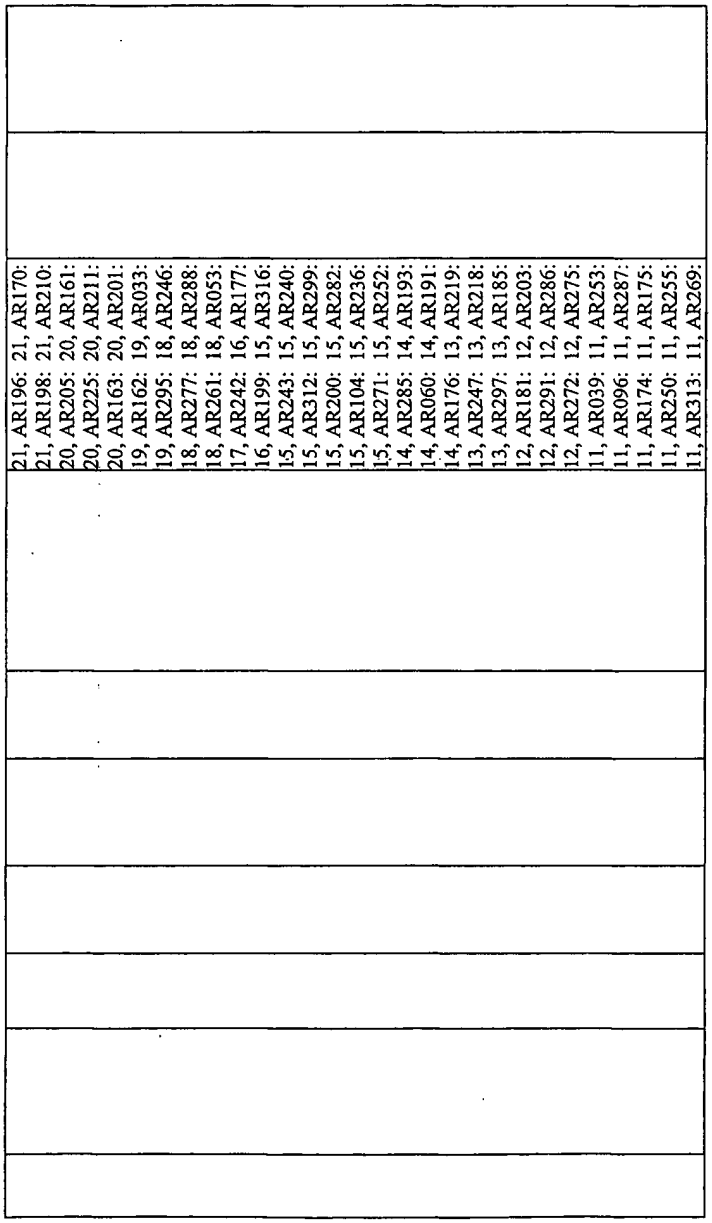
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68	HCE2B33	745399	78	67 - 234	171	Thr-18 to Cys-26, Glu-29 to Thr-36, Ser-50 to Thr-55.	AR254: 6, AR250: 6, AR039: 5, AR198: 5, AR165: 4, AR161: 4, AR176: 4, AR162: 4, AR180: 4, AR266: 4, AR163: 4, AR166: 4, AR164: 4, AR269: 4, AR168: 4, AR268: 4, AR181: 4, AR309: 4, AR252: 4, AR274: 4, AR242: 4, AR223: 4, AR172: 4, AR205: 3, AR282: 3, AR270: 3, AR207: 3, AR240: 3, AR216: 3, AR275: 3, AR296: 3, AR178: 3, AR238: 3, AR195: 3, AR277: 3, AR197: 3, AR173: 3, AR253: 3, AR289: 3, AR228: 3, AR183: 3, AR236: 3, AR104: 3, AR257: 3,	17q25	114290, 138033, 162100, 170500, 170500, 170500, 180860, 264470

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69	HDPBQ02	745403	79	460 - 786	172	Gln-30 to Leu-38, Asn-75 to Thr-86.	AR313: 17, AR281: 12, AR314: 12, AR241: 12, AR315: 12, AR164: 11, AR280: 11, AR292: 10, AR096: 10, AR263: 10, AR299: 9, AR249: 9, AR194: 9, AR300: 9, AR247: 9, AR265: 9, AR052: 8, AR089: 8, AR184: 8, AR312: 8, AR310: 8, AR229:	

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70	HFIYI70	744906	80	43 - 195	173		AR207: 47, AR263: 38, AR214: 35, AR223: 31, AR192: 30, AR264: 29, AR245: 28, AR235: 28, AR172: 27, AR222: 27, AR165: 26, AR169: 26, AR195: 26, AR213: 26, AR311: 25, AR217: 25, AR168: 25, AR224: 25, AR212: 25, AR164: 25, AR166: 25, AR221: 25, AR197: 25, AR309: 24, AR171: 24, AR216: 23, AR188: 23, AR308: 23, AR089: 21, AR215:	12	


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20, AR225: 20, AR211:
20, AR163: 20, AR201:
19, AR162: 19, AR033:
19, AR295: 18, AR246:
18, AR277: 18, AR288:
18, AR261: 18, AR053:
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71	HDPOZ56	815653	81	103 - 1800	174	Gln-22 to Gln-44, Ala-90 to Gly-95, Lys-137 to Trp-146, Arg-171 to Asp-181, Glu-370 to Ser-380, Asp-447 to Gly-452, Gln-463 to Trp-469, Asn-504 to Ala-510, Asp-512 to His-519, Ala-541 to Val-550, Asn-558 to His-566.	AR248: 20, AR253: 20, AR281: 16, AR244: 14, AR273: 13, AR202: 12, AR315: 12, AR310: 11, AR263: 11, AR224: 10, AR280: 10, AR194: 9, AR284: 9, AR223: 9, AR251: 9, AR165: 9, AR215: 9, AR265: 9, AR206: 9, AR198: 9, AR311: 9, AR164:		

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Table 1C

Gene No.:	Clone ID	Preferred Indication Identifier
1	HISCN02	Digestive
2	HHGDM70	Immune/Hematopoetic
3	HHPGO40	Cancer
4	HAMGG68	Cancer
5	HAPOM49	Cancer
6	HBGBA69	Cancer
7	HBJFJ26	Cancer
8	HCEDH38	Mixed Fetal, Neural/Sensory
9	HDPOJ08	Cancer
10	HDPRX82	Cancer
11	HELGK31	Cancer
12	HFPCX64	Mixed Fetal, Neural/Sensory
13	HFXDO60	Neural/Sensory
14	HHEPG41	Cancer
15	HKGAH42	Neural/Sensory
16	HMIAP86	Cancer
17	HMUAP70	Cancer
18	HRACJ35	Cancer
19	HTWDE26	Cancer
20	HUSIB13	Cancer
21	HBAFA02	Cancer
22	H2CBT75	Cancer
23	HAGDQ42	Cancer

24	HBMCJ42	Immune/Hematopoetic, Reproductive
25	HDPBQ71	Cancer
26	HCEJG71	Cancer
27	HELHL48	Cancer
28	HISAQ04	Digestive, Neural/Sensory, Reproductive
29	HJACB89	Cancer
30	HTECC05	Cancer
31	HBJLF01	Cancer
32	HBXGP60	Cancer
33	HCE5B20	Mixed Fetal, Neural/Sensory
34	HCMSQ56	Cancer
35	HCNAH57	Digestive
36	HCUEP91	Immune/Hematopoetic
37	HDPCJ91	Cancer
38	HDPGK25	Cancer
39	HE2DY70	Immune/Hematopoetic, Mixed Fetal, Musculoskeletal
40	HE2NV57	Cancer
41	HETBR16	Digestive, Immune/Hematopoetic, Reproductive
42	HFXDG13	Cancer
43	HFXKY27	Neural/Sensory

44	HHPEC09	Cancer
45	HISAD54	Cancer
46	HJBCY35	Cancer
47	HKAEA19	Cancer
48	HKGDL36	Cancer
49	HLDBS43	Cancer
50	HLWAD92	Cancer
51	HLYBI15	Immune/Hematopoetic
52	HMEJE05	Cancer
53	HNGIX55	Immune/Hematopoetic
54	HNHEX30	Immune/Hematopoetic
55	HPJBI33	Reproductive
56	HRABA80	Excretory
57	HRACD80	Excretory, Reproductive
58	HSLCX03	Cancer
59	HT5GJ57	Cancer
60	HTACS42	Cancer
61	HTEKE40	Cancer
62	HTOBX69	Cancer
63	HUVEO77	Reproductive
64	H2CBG48	Cancer
65	H2CBU83	Cancer
66	HAPNY94	Cancer
67	HBJHZ58	Immune/Hematopoetic, Reproductive
68	HCE2B33	Cancer

69	HDPBQ02	Immune/Hematopoetic
70	HFIYI70	Cancer
71	HDPOZ56	Cancer

Table 1D

Clone ID NO:Z	SEQ ID NO:X	CONTIG ID:	BAC ID: A	SEQ ID NO:B	EXON From-To
HISCN02	11	638033	AC012267	271	1-1102
HISCN02	11	638033	AL359715	272	1-1102
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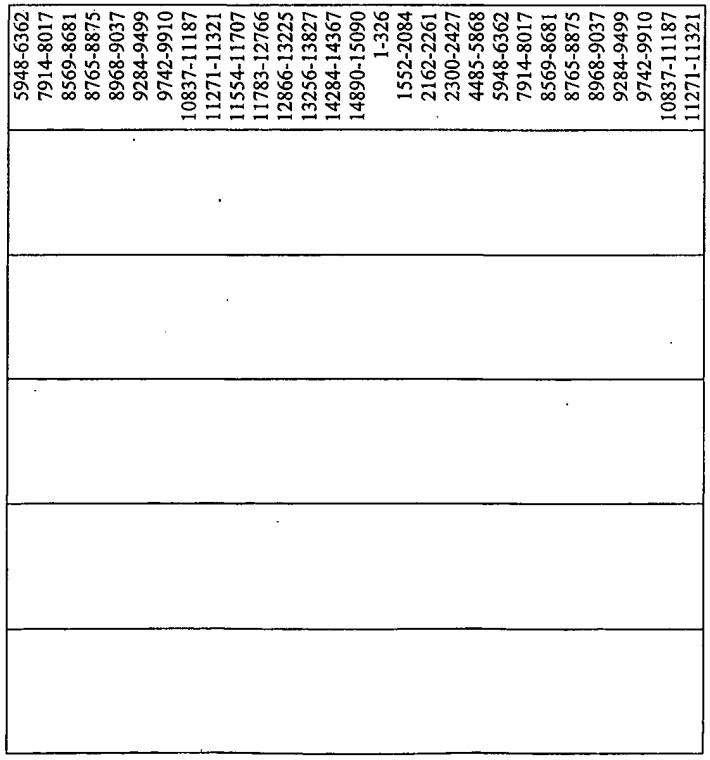
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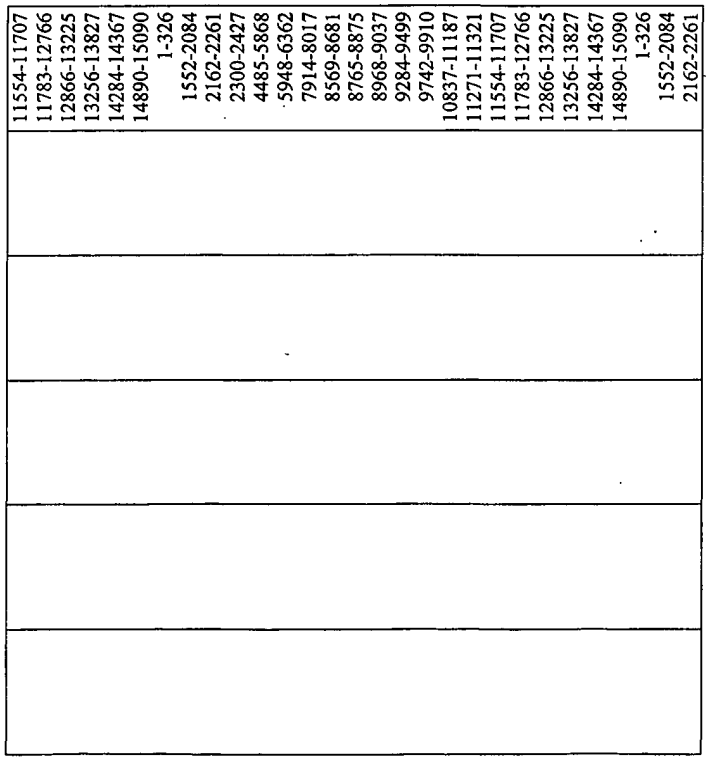
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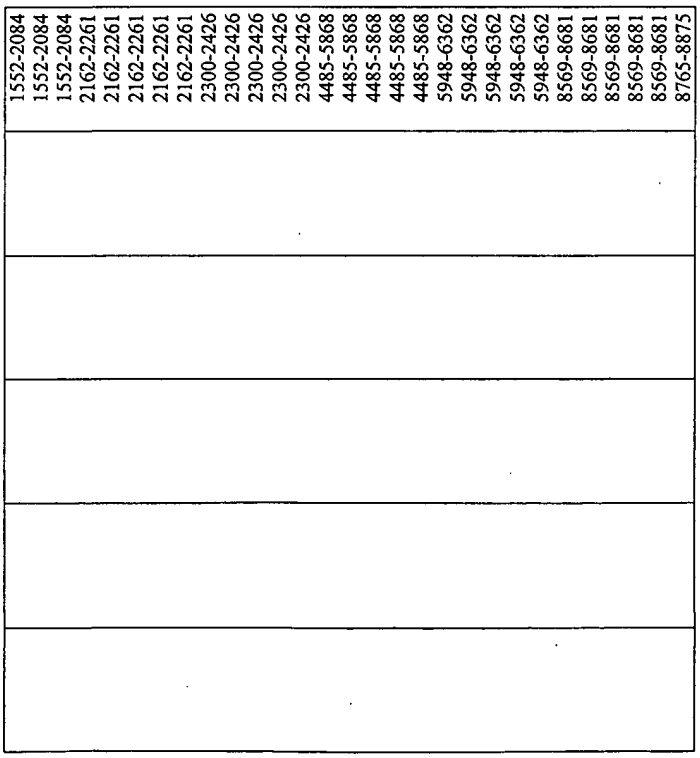
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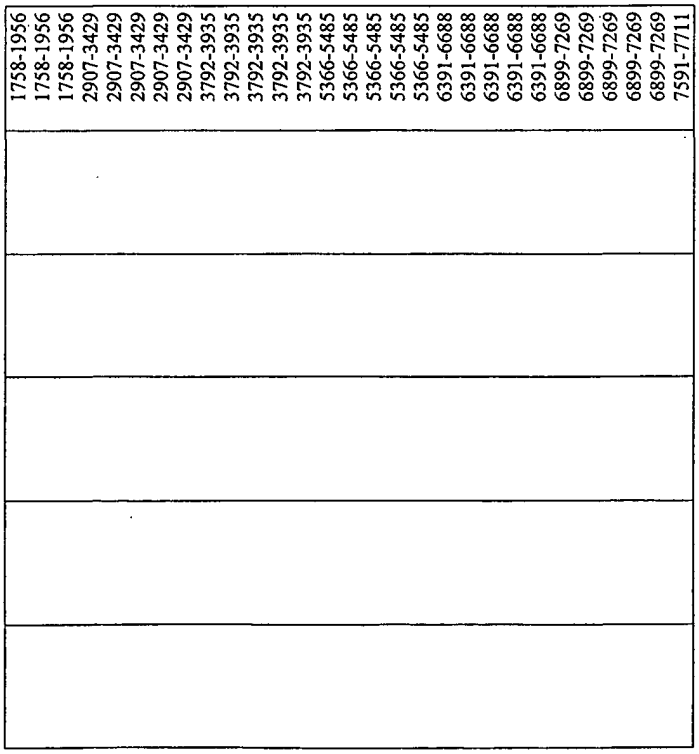
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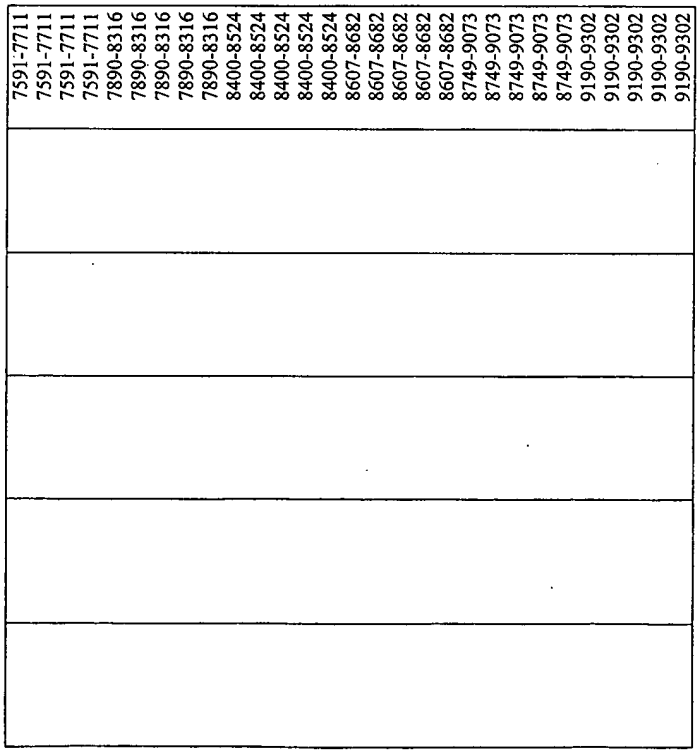
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HSLCX03	68	889145	AC035249	383	1-397
HSLCX03	68	889145	AC034258	384	1-648
HSLCX03	68	889145	AC027135	385	1-434
HSLCX03	68	889145	AC027035	386	1-624
HSLCX03	68	889145	AC027034	387	1-509
HSLCX03	68	889145	AC026815	388	1-654
HSLCX03	68	889145	AC025815	389	1-380
HSLCX03	68	889145	AC025781	390	1-546
HSLCX03	68	889145	AC018903	391	1-631
HSLCX03	68	889145	AC078894	392	1-654
HT5GJ57	69	740767	AC005081	393	1-149
					1029-1450
					4881-5071
					5302-5397
					6004-6132
					6888-6926
					7229-7329
					9066-9254
					9805-9848
					9852-10211
					10276-10315

					10619-10807
					10855-11472
					11695-11852
					12358-12468
					13770-13847
					14053-14259
					14695-14822
					16101-16553
					18233-18690
					18750-19965
HT5GJ57	69	740767	AC016675	394	1-149
					1029-1450
					1623-1790
					4908-5098
					5329-5424
					6031-6159
					6915-6953
					7256-7356
					9095-9306
					9834-9877
					9881-10239
					10304-10343
					10647-10835
					10883-11500
					11724-11881
					13799-13876
					14082-14288
					14725-14852
					16131-16583

					18262-18719 18757-19994 20161-20420
HT5GJ57	69	740767	AC005081	395	1-233
HT5GJ57	69	740767	AC016675	396	1-720 2099-2265 2776-3550 3946-4146 4976-5104 5781-6171 6476-7039 7384-7738 7837-8009 8434-8593 11644-11746
HTACS42	70	722253	AC010655	397	1-926 1359-3248
HTACS42	70	722253	AC010655	398	1-351
HTACS42	70	722253	AC010655	399	1-415
HTEKE40	71	740768	AC027430	400	1-1447
HTEKE40	71	740768	AL356216	401	1-1567
HTEKE40	71	740768	AC027430	402	1-101
HTEKE40	71	740768	AL356216	403	1-101
HUVEO77	73	740776	AC031977	404	1-169 5219-10427
H2CBU83	75	884134	AC022205	405	1-281 1126-1265 4567-4638

						4750-5149
						5194-5262
						6765-6837
						8311-8375
						9163-9234
						11487-11558
						11857-11984
						13132-13251
						13836-13920
						16388-19859
H2CBU83	75	884134	AC022205	406		1-630
H2CBU83	75	884134	AC022205	407		1-387
HAPNY94	76	699770	AL133351	408		1-238
						2679-2860
						6204-6544
						6911-7399
						7795-7909
						8430-8914
						9187-9620
						9744-10234
						11159-11190
						11310-11737
						12408-16037
HAPNY94	76	699770	AC013339	409		1-238
						2699-2880
						6224-6564
						6931-7419
						7815-7929
						8449-8932

					9205-9638 9762-10130 10144-10309 11380-11807 12478-16107
HAPNY94	76	699770	AL133351	410	1-466
HAPNY94	76	699770	AC013339	411	1-466
HBJHZ58	77	745372	AC022609	412	1-1817
HBJHZ58	77	745372	AC009925	413	1-1816
HBJHZ58	77	745372	AC022609	414	1-339
HBJHZ58	77	745372	AC009925	415	1-339
HDPBQ02	79	745403	AC020929	416	1-110 227-409 520-565 681-817 998-3175 3448-3612 3693-3784 3866-4063 5477-5596
HDPBQ02	79	745403	AC020929	417	1-384
HFIYI70	80	744906	AC023020	418	1-1656
HFIYI70	80	744906	AL353755	419	1-1656
HFIYI70	80	744906	AC023020	420	1-1152
HFIYI70	80	744906	AL353755	421	1-1152

Table 1E

Gene No.	cDNA Clone ID No:Z	AA SEQ ID NO: Y	Biological Activity	Exemplary Activity Assay	Preferred Indication
3	HHPGO40	106	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated

			368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.	immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic

					conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
3	HHPGO40	106	Upregulation of CD69 and activation of T cells	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells,	A highly preferred embodiment of the invention includes a method for

				B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of	activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for activation B cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating B cells. A highly preferred embodiment of the invention includes a method for activating NK cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting activation of and/or inactivation NK cells. Highly preferred indications include inflammation and inflammatory disorders (e.g., as described below under "Immune Activity").

				the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Ferenczi et al., J Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-	Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response and alternatively suppressing a T cell-mediated immune response, and boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. An additional highly preferred indication includes infection (e.g., as described below under "Infectious Disease"). Preferred indications also include anemia, pancytopenia,

			mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, inflammation and inflammatory disorders, asthma, and allergies. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal,

					stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
4	HAMGG68	107	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the	A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An

				assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.	alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenisis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment

				of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as

				well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as,

				prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenom, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from

				balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or

					""Cardiovascular Disorders""). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
5	HAPOM49	108	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below),

				Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or	diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section

				may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
6	HBGBA69	109	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage

			number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that	(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal

				may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
9	HDPOJ08	112	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel

				capase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that	blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture).

				may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin,and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.	An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
11	HELGK31	114	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells.	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g.,

				Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional	reducing) IL-6 production. A highly preferrred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include

				activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and	inflammation and inflammatory disorders.Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia,

				upregulate T cell proliferation and functional activities.	Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additonal preferred indication is infection (e.g., an infectious disease as described below under ""Infectious Disease"").
11	HELGK31	114	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression.	A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg. Highly preferred indications include blood

			Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention	disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic

				(including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These	pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous

				cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
12	HFPCX64	115	Production of IL-5	IL-5 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells, mast cells, basophils, and eosinophils that stimulate eosinophil function and B cell Ig production and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cell function, modulate B cell Ig production, modulate immune	A highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-5 production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-5 production. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) immunoglobulin production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) immunoglobulin production.

				cell polarization, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-5, and the stimulation of eosinophil function and B cell Ig production. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Ohshima et al., Blood 92(9):3338-3345 (1998); Jung et al., Eur J Immunol 25(8):2413-2416 (1995); Mori et al., J Allergy Clin Immunol 106(1 Pt 2):558-564 (2000); and Koning et al., Cytokine	A highly preferred indication includes allergy. A highly preferred indication includes asthma. A highly preferred indication includes rhinitis. An additional highly preferred indication is infection (e.g., an infectious disease as described below under ""Infectious Disease""), and inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under

				9(6):427-436 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	"Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, hemophilia,

					hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
16	HMIAP86	119	Production of TNF alpha by dendritic cells	TNFa FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFa), and the induction or inhibition of an inflammatory or cytotoxic response. Such	A highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and

				assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1198); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are	suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia,

				antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
16	HMIAP86	119	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T	A highly preferred embodiment of the invention includes a method for stimulating MIP1a production. An alternative highly preferred

				cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-	embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute

				204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic

					conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
16	HMIAP86	119	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications include autoimmune diseases

			differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation	(e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under

				and functional activities.	"Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
17	HMUAP70	120	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or

				SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.	""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example,

				leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkit's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis,

					meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
18	HRACJ35	121	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesisand its expression is stimulted by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-

			used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Iipenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362–368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or	hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively,

				may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
25	HDPBQ71	128	IL-2 in Human T cells		
25	HDPBQ71	128	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a	A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related

				variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays	Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g.,

				disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance	leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis,

				responsiveness to immunomodulatory factors.	suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
27	HELHL48	130	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell homeostasis and expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and	A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or

				agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin	""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative

				Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, inflammation and inflammatory disorders, and asthma and allergy. An additional preferred indication is infection (e.g., as described below under "Infectious Disease").
	HTECC05	133	Regulation of	Assays for the regulation of	A highly preferred

30			viability and proliferation of pancreatic beta cells.	viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari	indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders""

				MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
31	HBJLF01	134	Activation of transcription through AP1	Assays for the activation of transcription through the AP1 response element are known in	Preferred indications include neoplastic diseases (e.g., as described below under

			response element in immune cells (such as T-cells).	the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the	"Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms

				contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.	and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.
34	HCMSQ56	137	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may	Preferred embodiments of the invention include using polypeptides of the invention

				be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).	(or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Athereosclerosis, Restenosis, and Stroke
37	HDPCJ91	140	Activation of Skeletal Mucle Cell PI3 Kinase	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal	A highly preferred embodiment of the invention includes a method for

			Signalling Pathway	transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be	increasing muscle cell survival An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle

			used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.	cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under ""Endocrine Disorders""), neural disorders (e.g., as described below under ""Neural Activity and Neurological Diseases""), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under ""Immune Activity""), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes

					mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g, due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders""

				section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additonal highly preferred indications are disorders of the musculoskeletal system including myopathies,

					muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.
38	HDPGK25	141	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large	A highly preferred embodiment of the invention includes a method for

			variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J	stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred

				Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic,

					esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
39	HE2DY70	142	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and	A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or as

			agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad	described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma,

				Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
	HE2NV57	143	ATF-2 in CTLL-2	final_assay_desc	final_assay_embodiment

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40	HE2NV57	143	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997);	Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described

			Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.	below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis,

					meningitis, and Lyme Disease.
40	HE2NV57	143	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn	Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below

				et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.	under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune

					reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
40	HE2NV57	143	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of	Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include

			the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.	autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is

					idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
40	HE2NV57	143	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood

				factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell	disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative

			line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.	Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune

					reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
40	HE2NV57	143	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic

				component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that	neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or

				may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
40	HE2NV57	143	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2	A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention

				expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC).	includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune

			Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.	response, and suppressing a T cell-mediated immune response. An additional highly preferred indication includes infection (e.g., AIDS, and/or as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic

				conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. A highly preferred indication is infection (e.g., tuberculosis, infections associated with granulomatous disease, and osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL),

					plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
41	HETBR15	144	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein	Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Athereosclerosis, Restenosis, and Stroke

				incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).	
43	HFXKY27	146	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the

			invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3	invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under ""Endocrine Disorders""). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related

			fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	Disorders"), immune disorders (e.g., as described below under ""Immune Activity""), neural disorders (e.g., as described below under ""Neural Activity and Neurological Diseases""), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental

				confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively,

				weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications

					include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
43	HFXKY27	146	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies	Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.

			and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.	Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatosus disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional

					preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
46	HJBCY35	149	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as

				proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays	described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and

				are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
46	HJBCY35	149	Activation of Skeletal Mucle Cell PI3 Kinase Signalling Pathway	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survivial are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	A highly preferred embodiment of the invention includes a method for increasing muscle cell survival An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell

			promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle,	proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under

			that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.	"Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under ""Endocrine Disorders""), neural disorders (e.g., as described below under ""Neural Activity and Neurological Diseases""), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under ""Immune Activity""), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as

				described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g. due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and

				disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additonal highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest,

					heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.
48	HKGDL36	151	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below),

			Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or	diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section

				may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
55	HPJBI33	158	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage

			upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC)	(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal

				and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
56	HRABA80	159	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve

			pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be	disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the

				used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HITT15 Cells. HITT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
56	HRABA80	159	Activation of Endothelial Cell ERK Signaling Pathway.	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation	A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly

				are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Berra et al., Biochem Pharmacol 60(8):1171-1178 (2000); Gupta et al., Exp Cell Res 247(2):495-504 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which	preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention

				are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.	includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell differentiation. A highly preferred embodiment of the invention includes a method for stimulating angiogenisis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly

				preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins

				and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and

				urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenom, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atheroschlerotic lesions), implant fixation, scarring,

				ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Preferred indications include autoimmune diseases (e.g.,

					rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
56	HRABA80	159	Upregulation of CD152 and activation of T cells	CD152 FMAT. CD152 (a.k.a. CTLA-4) expression is restricted to activated T cells. CD152 is a negative regulator of T cell proliferation. Reduced CD152 expression has been linked to hyperproliferative and autoimmune diseases. Overexpression of CD152 may lead to impaired immunoresponses. Assays for immunomodulatory proteins important in the maintenance of T cell homeostasis and	A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. An alternative highly preferred embodiment of the invention

			expressed almost exclusively on CD4+ and CD8+ T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, maintain T cell homeostasis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD152, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al.,	includes a method for stimulating T cell proliferation. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example,

				""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); McCoy et al., Immunol Cell Biol 77(1):1-10 (1999); Oostervegal et al., Curr Opin Immunol 11(3):294-300 (1999); and Saito T, Curr Opin Immunol 10(3):313-321 (1998), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, inflammation and

					inflammatory disorders, and asthma and allergy. An additional preferred indication is infection (e.g., as described below under "Infectious Disease").
57	HRACD80	160	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include

			polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and diffferentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); and Verhasselt et al., J	autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders.Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma,

			Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additonal preferred

					indication is infection (e.g., an infectious disease as described below under ""Infectious Disease"").
59	HT5GJ57	162	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA	Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications

			85:6342-6346 (1988); Reillahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.	also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression

					of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.
59	HT5GJ57	162	Production of MCP-1	MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications

			test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Satthaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and	include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as

				upregulate T cell proliferation and functional activities.	described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
64	H2CBG48	167	Activation of transcription through AP1 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the AP1 response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the AP1 response element that may be used or routinely	Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include

				modified to test AP1-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the HT2 cell line, which is an IL-2	autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.

				dependent suspension culture cell line that also responds to IL-4.	Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.
64	H2CBG48	167	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell	Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple

			functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the HT2 cell	sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and

				line, which is a suspension culture of IL-2 dependent T cells that also respond to IL-4.	pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
65	H2CBU83	168	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion.	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other

			For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein	diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection

				incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	(e.g., infectious diseases and disorders as described in the ""Infectious Diseases"" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.
66	HAPNY94	169	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting

				of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety.	adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under ""Endocrine Disorders""). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under

				Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	"Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under ""Immune Activity""), neural disorders (e.g., as described below under ""Neural Activity and Neurological Diseases""), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other

					diseases and disorders as described in the ""Renal Disorders"" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the ""Cardiovascular Disorders"" section below), dyslipidemia, endocrine disorders (as described in the ""Endocrine Disorders"" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g.,

				infectious diseases and disorders as described in the ""Infectious Diseases"" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or

					disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
69	HDPBQ02	172	Upregulation of CD69 and activation of T cells	CD69 FMAT. CD69 is an activation marker that is expressed on activated T cells, B cells, and NK cells. CD69 is not expressed on resting T cells, B cells, or NK cells. CD69 has been found to be associated with inflammation. Assays for immunomodulatory proteins expressed in T cells, B cells, and leukocytes are	A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention

			well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate the activation of T cells, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the upregulation of cell surface markers, such as CD69, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include, for example, the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., ""Lymphocytes: a practical approach"" Chapter 6:138-160 (2000); Ferenczi et al., J	includes a method for activation B cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating B cells. A highly preferred embodiment of the invention includes a method for activating NK cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting activation of and/or inactivation NK cells. Highly preferred indications include inflammation and inflammatory disorders (e.g., as described below under "Immune Activity"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Highly preferred indications include autoimmune diseases

			Autoimmun 14(1):63-78 (200); Werfel et al., Allergy 52(4):465-469 (1997); Taylor-Fishwick and Siegel, Eur J Immunol 25(12):3215-3221 (1995); and Afetra et al., Ann Rheum Dis 52(6):457-460 (1993), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.	(e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response and alternatively suppressing a T cell-mediated immune response, and boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. An additional highly preferred indication includes infection (e.g., as described below under "Infectious Disease"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia,

					neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, inflammation and inflammatory disorders, asthma, and allergies. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
	HDPOZ56	174	Activation of	Assays for the activation of	Preferred embodiments of the

71			transcription through GAS response element in epithelial cells (such as HELA cells).	transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: You M, et al, J Biol Chem, 272(37):23376-23381(1997); Min W, et al., Circ Res, 83(8):815-823 (1998); Berger et al., Gene 66:1-10 (1998); Cullen and	invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Cancer, Wound Healing, and Inflamation. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include inflammation and inflammatory disorders.

				Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Epithelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary epithelial cells that may be used according to these assays include the HELA cell line.	
71	HDPOZ56	174	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including	A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred

				antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g.,	embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells.

			through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.	A highly preferred embodiment of the invention includes a method for stimulating angiogenisis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular

				disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications

				include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenom,

				aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atheroschlerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular

				degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or ""Cardiovascular Disorders""). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain


management.

Table 2

Clone ID NO:Z	Contig ID:	SEQ ID NO:X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/ Percent Identity	NT From	NT To
HISCN02	638033	11	WUblastx.64	(AF116695) PRO2221 [Homo sapiens]	gb|AAF71115.1|AF116721_95	56%	930	1109
HHPGO40	753270	13	HMMER 2.1.1	PFAM: Leucine Rich Repeat	PF00560	122	542	613
			WUblastx.64	(AF196976) brain tumor associated protein NAG14 [Homo sapiens]	gb|AAG28019.1|AF196976_1	70%	233	967
HHPGO40	560969	82	HMMER 2.1.1	PFAM: Leucine Rich Repeat	PF00560	77	548	619
HAMGG68	731859	14	blastx.2	CDNA FLJ20378 FIS, CLONE KAIA0536.	sp|Q9NX85|Q9NX85	64% 71% 56% 44% 47% 57% 70%	857 984 726 1454 1454 1457 1458	636 859 658 1401 1392 1416 1429
HAPOM49	769555	15	WUblastx.64	(AF306567) group XII secreted phospholipase A2 [Homo sapiens]	gb|AAG50243.1|AF306567_1	91%	305	817
HBJFJ26	772348	17	WUblastx.64	(BC000168) Unknown (protein for MGC:5242) [Homo sapiens]	gb|AAH00168.1|AAH00168	77%	1166	831
HDPOJ08	731863	19	blastx.2	CDNA FLJ14153 fis,	sp|BAB14852|BAB	99%	12	524

				clone NT2RM1000092, weakly similar to 1	14852	85% 46% 30%	524 763 315	904 900 479
HDPRX82	730518	20	blastx.2	(AF336887) FKSG60 [Homo sapiens]	gb|AAK01738.1|AF336887_1	68%	1521	1724
HELGK31	681138	21	HMMER 2.1.1	PFAM: DHHC zinc finger domain	PF01529	95.1	659	820
			blastx.2	CDNA FLJ10479 FIS, CLONE NT2RP2000120 (DC1).	sp|Q9NPG8|Q9NPG8	99%	209	1240
HCNUA40	340352	85	HMMER 2.1.1	PFAM: DHHC zinc finger domain	PF01529	95.1	-82	-243
			blastx.2	CDNA FLJ10479 FIS, CLONE NT2RP2000120 (DC1).	sp|Q9NPG8|Q9NPG8	100% 98% 36%	845 1101 1307	69 847 1215
HFPCX64	877637	22	WUblastx. 64	(AK025047) unnamed protein product [Homo sapiens]	dbj|BAB15056.1|	54% 56%	891 1064	781 870
HCEBW71	514187	87	blastx.2	(AF000996) ubiquitous TPR motif, Y isoform [Homo sapiens]	gb|AAC51843.1|	56%	1125	859
HFXDO60	731869	23	WUblastx. 64	(AL035587) dJ475N16.1 (CTG4A) [Homo sapiens]	emb|CAB75301.1|	68% 86% 83%	306 1176 771	88 1024 643
HHEPG41	714102	24	blastx.2	(AF059620) My006 protein [Homo sapiens]	gb|AAG43119.1|AF059620_1	100%	406	723
HAUAI83	639009	88	blastx.2	(AF059620) My006 protein [Homo sapiens]	gb|AAG43119.1|AF059620_1	88% 100%	160 489	399 557

						90%	25	84
HJPAZ83	383592	89	blastx.2	(AF059620) My006 protein [Homo sapiens]	gb|AAG43119.1|AF059620_1	100%	671	354
HMIAP86	726831	26	HMMER 2.1.1	PFAM: Mitochondrial carrier proteins	PF00153	262	329	1180
			blastx.2	BRAIN MITOCHONDRIAL CARRIER PROTEIN-1 (BMCP-1) (SOLUTE CARRIER FAMILY 25, MEMBER 14).	sp|O95258|BMCP_HUMAN	97%	182	1183
HMUAP70	872208	27	blastx.2	(AF220209) Nedd4 WW domain-binding protein 5 [Mus musculus]	gb|AAG44248.1|	89%	69	845
HAGFY16	778820	91	blastx.2	(AF220209) Nedd4 WW domain-binding protein 5 [Mus musculus]	gb|AAG44248.1|	69% 45%	56 31	844 402
HAGFY16	381964	94	blastx.2	(AF220209) Nedd4 WW domain-binding protein 5 [Mus musculus]	gb|AAG44248.1|	86%	1830	1111
HRACJ35	730504	28	WUblastx.64	(AF119386) blood plasma glutamate carboxypeptidase 1	gb|AAD31418.1|AF119386_1	65% 99%	1486 99	1722 1439
HAWAZ34	470546	95	blastx.2	AMINOPEPTIDASE.	sp|Q9Y646|Q9Y646	100% 96%	1134 628	616 350
HTWDE26	668265	29	blastx.2	C11ORF15 PROTEIN.	sp|Q9NQ34|Q9NQ34	100% 100%	173 68	568 151
HMHBN40	638249	96	blastx.2	C11ORF15 PROTEIN.	sp|Q9NQ34|Q9NQ	89%	129	650

					34	100% 73%	652 680	693 724
HUSIB13	580885	30	blastx.2	DYSFERLIN.	sp|O75923|O75923	100%	25	309
H2CBT75	703079	32	blastx.2	CDNA: FLJ21463 fis, clone COL04765.	sp|BAB15071|BAB 15071	72%	318	611
HAGDQ42	702035	33	blastx.2	HSPC327 (FRAGMENT).	sp|Q9P055|Q9P055	99% 100%	33 10	869 33
HBMCJ42	713345	34	HMMER 2.1.1	PFAM: Lectin C-type domain	PF00059	19.4	-297	-566
			WUblastx. 64	(AK016908) putative [Mus musculus]	dbj|BAB30491.1|	28%	1545	775
HDPBQ71	1160316	35	blastx.2	CDA08.	sp|AAG41782|AA G41782	95% 65% 44%	114 97 110	1928 192 250
HDPBQ71	727200	97	blastx.2	CDA08.	sp|AAG41782|AA G41782	95% 65% 44%	45 28 41	1859 123 181
HDPFQ90	886067	98	blastx	predicted using Genefinder; cDNA EST yk281d4.5 comes from this 1 comes from this gene [Caenorhabditis elegans]	emb|CAA77450.1|	38% 29% 31% 52% 58% 47% 25% 52% 45% 38% 34%	1790 1658 921 306 1356 480 1158 639 1464 783 321	1999 1945 1091 362 1406 536 1241 701 1523 860 398

						38% 30% 26% 38% 36% 29% 40% 30% 31%	1173 1104 798 1170 897 903 1341 324 2258	1265 1211 875 1223 995 995 1415 392 2305
HCEJG71	715592	36	HMMER 2.1.1	PFAM: WD domain, G-beta repeat	PF00400	79.1	265	381
			WUblastx. 64	(AF097484) transducin beta-like 2 [Homo sapiens]	gb|AAF06823.1|AF097484_1	89%	28	1368
HELHL48	696945	37	HMMER 2.1.1	PFAM: DHHC zinc finger domain	PF01529	124.3	797	991
			blastx.2	hypothetical protein DKFZp761E1347.1 - human (fragment)	pir|T47144|T47144	100%	359	1501
HSKCT36	610025	99	HMMER 2.1.1	PFAM: DHHC zinc finger domain	PF01529	124.3	199	393
			blastx.2	hypothetical protein DKFZp761E1347.1 - human (fragment)	pir|T47144|T47144	100% 99% 100%	10 585 470	471 905 586
HISAQ04	589960	38	blastx.2	CDNA FLJ20378 FIS, CLONE KAIA0536.	sp|Q9NX85|Q9NX85	56% 65% 46% 70%	1159 972 1157 1161	968 850 1086 1132

HJACB89	689899	39	WUblastx.64	(AK011230) putative [Mus musculus]	dbj|BAB27480.1|	93%	92	1093
HBJLF01	732111	41	HMMER 2.1.1	PFAM: Transmembrane 4 family	PF00335	131.8	223	891
			blastx.2	TETRASPANIN 5 (TSPAN-5) (TETRASPAN NET-4).	sp|O60628|TSN5_HUMAN	43%	151	894
HBXGP60	566892	42	blastx.2	hypothetical protein AAB71662.1 - human (fragment)	pir|T03307|T03307	40%	10	549
HCE5B20	544507	43	blastx.2	retrovirus-related pol polyprotein pseudogene - human 1	pir|A26718|A26718	33%	610	23
HCNAH57	694610	45	blastx.2	LINE-1 ELEMENT ORF2.	sp|O62658|O62658	41% 44%	255 362	16 261
HDPCJ91	740748	47	blastx.2	CDNA FLJ20489 FIS, CLONE KAT08285.	sp|Q9NX17|Q9NX17	74% 68% 42%	2372 2545 1570	2548 2685 1674
HDPGK25	704067	48	blastx.2	CDNA: FLJ22233 fis, clone HRC02016.	sp|BAB15271|BAB15271	98%	3	701
HE2DY70	722217	49	blastx.2	SIMILAR TO RING-H2 FINGER PROTEIN RHA1A.	sp|Q9SNH1|Q9SNH1	75%	638	543
HE2NV57	740750	50	blastx.2	BK445C9.3 (HIGH-MOBILITY GROUP (NONHISTONE CHROMOSOMAL) 1	sp|Q9UGV6|Q9UGV6	31% 66%	321 71	866 106
HETBR16	703243	51	blastx.2	(AB055298) hypothetical	dbj|BAB21923.1|	75%	99	1

				protein [Macaca fascicularis]				
HFXDG13	657390	52	blastx.2	HYPOTHETICAL 149.0 KDA PROTEIN.	sp|Q15606|Q15606	75% 64% 70% 80% 76% 58% 24% 81%	368 1097 832 552 1144 617 823 40	15 768 575 364 1094 552 677 8
HFXKY27	634161	53	blastx.2	CDNA: FLJ21394 fis, clone COL03536.	sp|BAB15056|BAB 15056	46% 63% 87%	936 821 763	814 765 716
HISAD54	740754	55	blastx.2	spliceosome-associated protein SAP-49 - human	pir|A54964|A54964	46% 35% 52%	1331 1750 1938	1095 1472 1876
HJBCY35	719729	56	blastx.2	hypothetical protein DKFZp586J0619.1 - human (fragment)	pir|T08758|T08758	100%	1	1212
HKAEA19	721489	57	blastx.2	SEVEN TRANSMEMBRANE PROTEIN TM7SF3.	sp|Q9NS93|Q9NS9 3	99% 97%	321 83	1520 328
HKGDL36	704088	58	blastx.2	PROSAAS PRECURSOR.	sp|Q9UHG2|Q9UH G2	82% 49%	99 55	830 555
HLDBS43	722228	59	WUblastx. 64	(AF225417) 88.8 kDa protein [Homo sapiens]	gb|AAG09719.1|AF 225417_1	82% 99% 35% 96%	1163 1512 597 13	1438 1967 656 1161

HLWAD92	695736	60	blastx.2	SH3-CONTAINING PROTEIN SH3GLB2.	sp|Q9NR46|Q9NR46	100%	1	351
HLYBI15	645262	61	blastx.2	PRO0483 PROTEIN.	sp|Q9UI58|Q9UI58	55% 75%	144 71	64 24
HMEJE05	722231	62	WUblastx.64	(AF168711) x 010 protein [Homo sapiens]	gb|AAF87313.1|AF168711_1	96%	25	816
HNGIX55	695749	63	blastx.2	CDNA FLJ11736 fis, clone HEMBA1005468.	sp|BAB13899|BAB13899	66%	379	717
HPJBI33	685699	65	blastx.2	NEURONAL THREAD PROTEIN AD7C-NTP.	sp|O60448|O60448	49% 50% 53% 52% 42% 59% 34% 51% 56% 52% 35% 37% 47% 90% 33% 85%	617 3 701 137 750 154 633 24 877 155 41 659 886 805 1317 904	934 146 817 256 899 234 890 122 945 256 256 925 942 834 1415 924
HRABA80	588460	66	WUblastx.64	(AK022184) unnamed protein product [Homo sapiens]	dbj|BAB13980.1|	50% 68%	237 311	296 445
	882163	67	HMMER	PFAM: EGF-like domain	PF00008	64.3	1337	1441

HRACD80			2.1.1					
			WUblastx.64	(AJ306906) fibulin-6 [Homo sapiens]	emb|CAC37630.1|	44%	695	1861
						37%	32	1441
						45%	1277	1915
						42%	1286	1579
						47%	1286	1525
HRACD80	740762	100	blastx.2	(AF135253) fibulin-2 [Mus musculus]	gb|AAD34456.1|	33%	898	1581
						31%	1279	1893
						45%	1279	1608
						49%	681	911
						44%	898	1125
						30%	901	1605
						43%	928	1149
						31%	802	1137
						43%	699	899
						35%	690	998
						41%	928	1119
						42%	699	911
						41%	699	908
						48%	699	890
						43%	699	914
						33%	1339	1533
						36%	898	1137
						30%	540	995
						33%	699	893
						37%	699	890
						43%	777	899
						46%	925	1002
						28%	898	1065

						33% 26% 31% 27% 36% 24% 23% 70% 35%	493 576 952 807 943 699 1057 1066 928	609 890 1125 1061 1041 869 1218 1095 1053
HSLCX03	889145	68	blastx.2	CDNA: FLJ21792 fis, clone HEP00441.	sp|BAB15133|BAB15133	99%	803	2605
HSLCX03	740788	101	blastx.2	(AL132954) putative protein [Arabidopsis thaliana]	emb|CAB75750.1|	37% 23% 32%	65 1578 1389	637 2102 1631
HT5GJ57	740767	69	WUblastx.64	(AX083396) unnamed protein product [Homo sapiens]	emb|CAC33299.1|	84%	122	856
HTACS42	722253	70	blastx.2	HYPOXIA-INDUCIBLE PROTEIN 2.	sp|Q9Y5L2|HIG2_HUMAN	100%	213	401
HTOBX69	722255	72	blastx.2	CGI-90 PROTEIN.	sp|Q9Y398|Q9Y398	94%	9	122
HUVEO77	740776	73	blastx.2	MSTP032.	sp|AAG39283|AAG39283	98%	1834	2082
H2CBU83	884134	75	WUblastx.64	(AF257182) G-protein-coupled receptor 48 [Homo sapiens]	gb|AAF68989.1|AF257182_1	89%	10	777
HCE2B33	745399	78	blastx.2	CDNA: FLJ22160 fis, clone HRC00266.	sp|BAB15242|BAB15242	91%	9	443

HDPBQ02	745403	79	WUblastx.64	(AK025047) unnamed protein product [Homo sapiens]	dbj|BAB15056.1|	60% 70% 38% 40% 67%	1759 2149 1828 1652 2022	1646 2021 1652 1548 1858
HFIYI70	744906	80	blastx.2	UNNAMED PROTEIN PRODUCT.	sp|Q9N0E1|Q9N0E1	97%	74	208
HDPOZ56	815653	81	HMMER 2.1.1	PFAM: Flavin containing amine oxidase	PF01593	431.1	307	1614
			blastx.2	Fig-1 protein [Mus musculus]	gb|AAB51353.1|	69%	169	1740
HDPOZ56	743479	103	HMMER 2.1.1	PFAM: Flavin containing amine oxidase	PF01593	185.2	200	949

Table 3

Clone ID NO: Z	SEQ ID NO: X	Contig ID:	EST Disclaimer Range of a	Range of b	Accession #'s
HISCN02	11	638033	1 - 1099	15 - 1113	BE791374, AU119289, AU140348, AU138078, AU136503, AV731936, AW840410, AL043065, AW840411, AW840407, AW840402, AW840408, AW840465, AW840466, AW840412, AW840471, AW840475, AW840473, AW814395, BF940866, BF056457, AA180278, AW840474, AA584866, BG005346, AW840406, AA569180, AV745684, AW270592, AA584638, AA976391, AV745320, AI820994, AA641592, BF195071, AI868368, BF931499, AA640504, BE797641, AV730261, AA258511, AW273171, AA457653, AA593381, AA584801, AW273229, AI052560, AV706319, AI800268, AA121904, AA664366, AA657354, BF954682, AI922061, BF513924, BE019309, AW939910, BE062393, T62761, AL044254, BF949385, AV701925, AA084302, AA601152, BF125684, AA121903, BF945554, AV652861, AW840551, BF946623, AV655231, AA584437, AW238615, AI061445, AA333509, F33455, BE439566, T66926, AL135706, AL044209, BE159332, AI349954, AA487808, AA481809, AW231969, AA720764, BE304382, AL359715, AL161627,

				AL390146, AL354833, AC068323, Z77249, AL139279, AL353633, AC010180, AC000055, AC010251, AL050401, AC006566, AL022157, AC074191, AL157830, AC006481, Z82211, AL136308, Z73913, AC004894, AC004470, AC007970, AL121755, AL160413, AC002454, AF003530, AC006120, AC007690, AC002449, AC025920, AC007286, AC024162, AC026197, AL136164, AC008250, AL121984, AL359641, AL109920, AL109761, AL023875, AL109764, AC011294, U69730, AC016626, AC004415, AL161804, AL133417, AC022143, AC016572, Y10196, AC005094, AC007032, AP001671, AL049859, AL132633, AC004842, AL359457, AC019058, AL360272, AC024084, AL359924, AL133412, AC012611, AC005230, AK002154, AC008550, AL157384, AC004677, AC012472, AC007683, AC008179, AC004959, AL031286, Z95124, AC007065, AC000378, AC004908, AL121782, AC005076, AL022345, U82828, AC005490, AL121983, AL445466, AC005034, AC005201, AC008664, AL359846, AK002104, AL133547, AL080275, AL133500, AC017092, AL033521, AL121825, AL023806, AC063976, AK023417, AL121575, AC027663, AP002532, AL138816, AC005386, AL121977, U40455, AL133516, AK024354, AC008462, AF235097, AL137022, AC003658, Z98255, AL161621, AC009230, AF101874, AC023478, AL031663, AL391691, AC026188, AL078597, AL034377, AC000119, AC034195, Z82899,

				AP001818, AL031274, AL157765, AL353999, AC011299, AP000692, AL136520, AL445472, AL359755, AL022241, AL357141, AL136147, AC016689, AL158841, AL121717, AC008009, AL121916, AF241732, AL161422, AK023839, AL139123, AL031114, AC002463, AC010282, AP001725, AC007327, AL139233, AL139375, AC008266, AL035252, AL035671, AC005823, AC006249, AC010596, AL359833, AL365400, AL161751, AC004628, AC006461, AL133325, AF044083, AC006265, Z83848, AC007745, Z68280, AC005064, AC016831, AC008583, AL031116, AL031347, AL390759, AL109915, AL138759, AL031673, AC009487, AC010369, AL033517, AL158206, AL049778, AL035699, AC005029, AC004852, AC006042, AC024576, AC004454, AL121867, AC006043, AP002023, AC008176, AC005019, AP002026, AC007748, AC003075, AL035563, AC004535, AC004948, U01882, AC005922, AL049794, AL121999, AC000125, AC013412, AB020861, AC006364, AB037817, AL355792, AK021968, AC016678, AL354793, AC016623, Z82210, AC021998, AC003986, AC008162, AL138478, AC006994, Z83745, AC005859, AC012312, AC008496, AL096803, AL133162, AF265340, AC009503, AL355294, AL021068, AL353614, Z80774, AE000659, AC008436, AC008394, AC073607, Z84720, AC009506, AC007253, AL356438, AC008897, AL359715, AL359715, AC012267, and AC012267.

HHGDM70	12	623416	1 - 969	15 - 983	AC019291, AC019291, AL157996, and AL157996.
HHPGO40	13	753270	1 - 959	15 - 973	BF936014, BF926087, BF849807, BG059559, AA663575, BE464797, and AL137451.
HAMGG68	14	731859	1 - 1444	15 - 1458	AW973341, AW974201, AL041477, AW471262, AV696883, AI799683, AI983869, AA579632, AI763280, AI962918, AW962479, AA919175, BE467860, AI694808, BE671481, BE670142, H97854, AA190313, AW608357, AV763623, AI656460, AI218288, AA057842, N39132, AA977897, AI907444, AI819548, AI698748, AI221889, AI300453, AA554290, BE327102, BF510243, AI366844, AI208651, AW341424, AW517375, AI092422, AI458704, AW770918, AA322568, H97652, AW058433, BG055320, T84069, AA587633, AI699024, BF881447, AW873347, AA397560, W46809, AI969771, AA807704, AA367835, R61770, AI819419, BF812696, BE882869, AL121039, AI702049, AA557945, AW148821, AA569220, AW118842, BF790866, AI567676, AW021674, AV683406, AI884404, BE875478, AW043803, AA935827, BG180320, BG059139, AI636422, AW265468, AW243817, AW162314, AW157128, AI439525, AI890283, AV743869, AW979200, AA805879, AW072963, AW162332, AI434103, H86399, AL134524, AA112864, AW576388, H47461, AW410844, AW192930, AL138262, AI445699, AI572680, BE049409, AV758849, AW029626, AW675677, AW575808, AU146789, BF725436, AI828721, BE045167, AW995605, AI860423, BG250794, AI888050, AI064968, BE065048, AV756809, AI547110, AV759204,

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HAPOM49	15	769555	1 - 1991	15 - 2005	AL520731, AL520732, BE271092, BE271295, BF111901, AV650049, BF686278, BE840511, BF111645, AI809801, AW168904, AI809806, AW103024, AA933973, AI744944, AI588991, AI033486, AI096548, AA662523, AW468813, AI950317, AI279302, AI096696, BF239172, AW662564, AA417671, AI189300, AI753808, AA235373, AW960081, AI095057, W86920, AW189373, AI361321, BF061913, AI366754, AI218487, AI824959, AI348339, AI032926, AV659024, AA889791, BE243641, AA626261, AI338100, AA417558, W24077, AW974720, N72014, AA894657, N59290, R01247, AA235784, BE929365, BE929364, BE244396, AI275184, AI810247, W24089, R36924, AA356938, N91904, AA508411, AA649828, N91912, N99466, Z24931, H68902, BE782571, BF840140, and AC004067.
HBGBA69	16	709658	1 - 929	15 - 943	AL520551, AL521649, AL520900, AL520550, BG029889, AV704088, AW372721, AA779652, BE782595, AL037829, BE906201,

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HBJFJ26	17	772348	1 - 1489	15 - 1503	AI222486, and AL521648. AL522907, AL526811, AL528580, BE619639, BE798341, BE785683, BF036910, AI816714, AW410741, AW675663, AA226255, AI077876, AA813934, AI354477, AW410740, AL522908, AA906037, BF038884, BG030252, N53061, AW440434, AA134769, AA037624, AL526841, AA641954, AI302550, AA424016, AA134768, AW074122, AA709434, AA424082, AI206461, AW074284, AI813620, BF824919, AI241581, W93593, AW814771, AA911289, BE898093, AI218492, AW504945, AI612865, BE869464, BE732878, BE734483, AI277607, AI187313, AI350811, AI434025, AW275190, AW276616, AA954030, BE731318, AW439574, BE731332, AI202853, AI004585, BE396498, AI265804, BF353710, N73248, AI244408, BE731484, AI241127, AA226533, R02524, BG110816, BE619122, AA037625, BE711537, H14806, AI954356, BF972886, AW193200, BE513950, BE300852, AA973778, AA876151, AA872499, AA010653, R29049, AA873196, AW629350, BF903325, BE280013, AA216115, BE177689, BF755890, BF756605, BF335325, BF088300, C02093, AA609581, AW016529, AA580145, AA760741, AI283813, AI096744, AU156247, N26872, AA057074, AI678948, N20594, AA486563, AA948624, AA535449, AA917667, AW015508, BE383689, BE877188, AW148479, AW802992, AI823982, F29139, F26541, F37068, BF526777, T96318, AI817412, BG255083, AK026103, AC009542, AC083862,

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HCEDH38	18	730529	1 - 1498	15 - 1512		AI632101, R15913, BG056741, AI880223, R43424, BF512075, BF515216, AW020619, Z99716, AK026597, AF126247, T66539, Z99716, and Z99716.
HDPOJ08	19	731863	1 - 1641	15 - 1655		BF968799, BF791555, AL513581, BE879926, AI949941, BE827843, BF968555, AI765763, BE875907, AW959968, AW382167, BF692458, BE876162, BF106234, AV713629, AV699640, AW382174, AU136532, BF692025, AA449500, AW902068, AW583040, BF212019, AW382170, AI768711, AI918137, AW235520, AI199832, AI074542, AA243341, AA071031, AL513582, AI308913, BE150978, AW609396, AA604828, AA831297, AI304674, BE151243, AW391610, AA704776, BE150919, AU155999, AW389522, AA878385, BF979062, BE150848, BE150932, AA554171, AI086256, AI285140, W48831, AW379916, BF215357, AW389518, AI361484, AI290204, BE150880, AA679730, AA285176, AI367820, BF570762, AA287652, AI028778, AI342266, AI332795, BE501465, AW609661, AA564884, AA497006, BF432681, BF438907, AA496929, AI742352, BF572848, AA824372, AW582335, AA286805, AA809400, AA101705, BE150881, H50009, AI356809, AI863722, AA449072, AW394227, N64570, BE614989, H66597, BE465872, AU157281, BF792958, AW394207, BE702178, AI860155, BE702109, T96603, BF792810, AW802638, H47883, BE702071, AW391634, AA425753,

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HDPRX82	20	730518	1 - 2511	15 - 2525	AL049055, BF684025, BF685956, BF683783, BF684251, BF683860, BF213335, AW816387, BF684265, AW857593, AW963304, AU123401, AA708837, BF991664, BG260606, BE542196, BF984668, AW857605, W52520, BG171880, AW968995, AW811248, AA573159, BF918605, AW857610, BF106301, AI066622, AW861480, BE160856, AA703380, BF959941, AA393030, AW852367, AW835723, BF952274, BG255269, AW835647, AA489237, AA452329, BE160656, BE161095, N35802, AW867362, AA808909, BF904041, AV764658, AW867431, AA730994, AA465244, AA158019, BF947338, AI086954, AI536854, AI291714, AL041488, AI792502, AI792459, AI741024, H94823, W61198, AW838260,

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HELGK31	21	681138	1 - 1382	15 - 1396	AL519840, AL519839, BE379142, BE786389, BE796190, BG117991, AL524590, BE744597, BE909841, BE907873, AL043167, BE544763, BE740216, AL518390, AL529705, AW592682, AW874363, AI085412, AW958434, AU126873, BF132076, AA604374, BF541758, BF794982, BE545432, AA936378, AA161264, AA531252, BE563799, AW072533, AA639981, AA677594, AI138280, AA218539, N94446, AI363012, BF114843, AI083837, D51047, BF343738, AW499697, AA437204, AA132746, AV712240, AI086913, AA889889, AA161263, AA916429, AA142878, AL518389, AA810233, AA613892, AA424834, AA143152, AA603133, AA132651, H11615, AW367012, AI268931, AI955333, AA948407, AW327686, AA856621, AA227183, AA524602, BE537412, W30793, AA969047, BE875215, AU149648, R54573, H18393, AW080718,

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HFPCX64	22	877637	1 - 1055	15 - 1069	AW969544, AW972136, AA503871, AI272041, AW515225, H65747, BF935424, AC016025, AC016026, AC007845, AC005562, AC020904, AF165926,

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HFXDO60	23	731869	1 - 1644	15 - 1658	BE390699, BF346226, AL520941, BG253282, BG032571, BE790095, AF150177, AI912465, AL520942, BG170667, AA292739, AA419155, BE250877, BF924799, BF901807, BE271697, BE891650, AL534026, AA639468, BF975546, BE790646, BF899941, BF973383, BF093166, BF093157, AL524222, AW889390, AI992170, BF903129, D63172, BE891409, W52850, BE250104, BE795572, BF882870, BE257602, BF093158, BF093167, BF744666, AA772406, AI040051, AI469599, AA527588, AI369580, AI870444, BG029528, AW515437, AA081727, AI499954, AW270771, BG222564, BG222326, AW780108, AA664604, AI962030, AI633168, BF992556, AA502991, AA720774, AW275971, T69638, AW188742, AA613624, AW979295, AW086291, AI754293, AL035587, AF161347, AL096791, AL118506, AL357497, AC011895, AC011465, AF196969, Z83822, AC005288, AL022237, AL109952, Z95115, AP000355, AC007386, AP000501, AC008745, AP000347, AC006057, AC007114, AC005399, AC020552, U85195, AC007225, AP000228, AC004961, AF038458, AL390738, AL109797, AP000512, AC010526, AL021707, AE000658, AC004882, AC005329, AL031658, AC006511, AC005522, AL138741, AC004149, AP000140, AL031672, AC006261, AC027319, Z97053,

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HHEPG41	24	714102	1 - 1063	15 - 1077	BE439675, BE903592, BF984328, BF337207, BF978147, AW955502, BE743902, BE272543, AV757236, BF212880, AW405217, AA889969, AI991315, AV701663, BE270100, BG178791, BF681301, BE222645, BG167626, BF238307, AW069149, BF680700, BF132414, BF698492, AV736544, BF130460, BG255905, AI493727, AV745093, BF102497, BE254068, AA934591, AI147316, BE543668, BG231583, BE256074, N24442, BE734398, AV754408, AW014782, AI198642, BE646408, AI709288, AA877730, AW135010, AI720901, AA496681, AA995328, AI032868, AI186312, AW579254, AI660672, AI969715, N23673, AI188938,

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HKGAH42	25	731871	1 - 1191	15 - 1205	BE840860.
HMIAP86	26	726831	1 - 1660	15 - 1674	AL533220, BF967956, AL533253, AL520510, BE735407, BF972030, BE735149, BE615619, BE616472, AI873527, BF347687, BE383692, BF967233, BE385645, AW593348, AW381588, BF541528, AI032869, BE294015, AA404241, AI564151, BE294088, AA401224,

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HMUAP70	27	872208	1 - 1951	15 - 1965	BE613319, AV687447, AV725712, AV687625, BG166531, BE612728, BG114876, AV686519, AW952404, AV725638, AI061630, BE877777, BF055022, BF439548, BF692350, BF732575, BF967994, BG054984, AW372569, BE866270, AW160677, AV706186, BF690981, AA813278, BF206792, BE876393, BE645016, AV728247, BF195583, AI612729, BF446480, BF210620, AW167859, AW167862, AA521082, BF445077, BF698977, BE348758, AW753532, AA161332, BF665995, BF195330, AI806813, AI887683, AA843967, AA525839, AI869290, AA447934, AW068627, BE881059, AI912708, AA843171, AW206294, BF673423, AA402367, AA910679, AA037122, AI091239, AI422091, AA287736, AI816253, AI802199, BE042949, W56256, AW156905, AA779099, AI057601, BG168894, BE327200, AA781082, AA496466, AW022886, AW275342, AI091181, BE218417, AA873496, AI290167,

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HRACJ35	28	730504	1 - 1849	15 - 1863	BE906771, BE218907, AI912661, BE670671, BG166321, AW167740, AI698131, AI796048, BF476110, AW952474, AW149683, AW474992, AI814137, BF436724, AI635719, AA452391, AI422285, AI675301, AW301634, AI800309, AI023300, AA054467, AI269915, BF062213, AI220479, AA991181, AI159765, AI623293, W88683, AI205308, AA043330, AA461136, BE669608, AI032982, AA634903,

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HTWDE26	29	668265	1 - 1612	15 - 1626	AL537331, BE883562, AI763238, BF111600, BF057137, AL537330, AI188389, AI188787, AA479523, AW338995, AW005918, BG033018, BE875058, AW583488, BG253636, AI346520, BF063112, AI423154,

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HUSIB13	30	580885	1 - 591	15 - 605		AW291051, AI862657, AI652465, AI310142, BE179051, BE463912, BE857013, BF966849, AW411174, R21727, AI888432, R76464, R63695, H25920, BF512300, H96393, BF512297, AI678163, AI918447, AI583737, BE161834, AI651879, AI493554, BF966293, AI650333, BF350444, BG251367, BE152158, BE152167, AW606124, R62744, AA968638, AW606135, AI193492, AW393675, H96036, BG013610, R76778, BE164321, BF090384, BF087510, AI262782, BE179223, BF993885, BE707209, BF090383, AF075575, and AJ007670.
HBAFA02	31	679555	1 - 917	15 - 931		BG028424, BF852127, AI084750, AU153708, AA398992, AA399627, AA402622, AI564897, AI083955, T03567, AI439461, AA729487, AI536788, AW364235, AW275187, AA999869, AI055824, AW364297, BF059669, W46460, AI198134, BG248314, BF814886, BE504806, AW274911, AW074663, AI652737, AU159564, BF738662, AI635013, AW364306, AL514829, AL513961, AL514773, AL515043, AL514757, AL514869, AL515375, AL514819, AL515035, AL514939, BF970652, AL515225, BG030750, AL514843, AI269580, AI538885, AL514885, AI648684, AL514763, AI632408, AL513977, BF815930, AW129106, BG036520, AL513817, AL513643, AI539153, AI783861, BF913616, AW054931, AI922561, AI355008, AL514357,

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H2CBT75	32	703079	1 - 1393	15 - 1407	BF308801, BF796401, AL120822, AA313583, AW772051, BF216725, BF769591, AA618422, BF769586, AA340511, BE138594, AV756809, AI754653, AA331298, AA410788, AI267356, AL041375, AW969743, AI267450, AV764259, BF925617, AA700014, AI040051, AU147162, AW968341, AA503298, AW575605, AW873061, AW976024, AI755202, AI066646, AV730824, BE676915, AW502796, AA570740, AA483606, AA578621, BG222875, AV763026, AV763058, AA228778, AV762633, AA468505, BF854244, AW268329, AA568204, BG250286, H38769, AI754170, AW271904, BF809041, AI537020, AA935409, AA455483, AI601229, BF997771, AA230025, AW069412, AW081303, AI251576, AI917132, AI798493, AW572159, AI732911, AA302812, AI306232, AW873261, AI056177, AA504818, AI821714, AF163573, AF168787, AL031584, AP002015, AC005913, AL050349, AC004962, AP000692, AL096801, AL138914, AC023510, AL031670, AC005971, AC020916, AC006270, AC004796, AC006515, Y10196, AC004966, AL035405, AL031427, AC008925, Z74739, AL008627,

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HAGDQ42	33	702035	1 - 1512	15 - 1526	BE877473, BF970684, BE748570, BF980024, BF983256, AU118684, AL035740, BF035136, BF790498, AI572580, AV728273, BE620517, N21200, BE620914, BF590374, BG104800, AU151320, AA447823, AA864616, AA813354, BF033632, AA805669, BE748156, AI755042, AV717005, AW021089, AW105200, BF575231, AU145187,

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HBMCJ42	34	713345	1 - 1723	15 - 1737	AV763804, AV700851, AV717615, AV700552, AI765451, AW467530, AV718709, BF510555, AW468273, AI674587, AI420431, AV682780, AW006869, AW192137, AI190626, AV646802, AI954636, AI655043, AI695965, BE242761, R19189,

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HDPBQ71	35	116031 6	1 - 2298	15 - 2312	AL517702, AL535136, AL517701, BF966919, AV712906, BF310001, BE785105, BG023779, AW608043, AW959115, AW571652, BE546297, AV733133, BG164317, BF965688, AA910337, AW070547, AA630221, AA936329, AI077660, N66596, AA233825, BF769251, AW169158, BE896148, AW966447, AI092899, AI804163, BF966148, AI184325, AI400074, AW105140, AI038519, BE178803, AI243767, AI803580, AA449258, AI089365, AI969422, AI292304, AA971310, AV753091, AA233729, AI289889, AI335939, AI275621, AV748056, BF828492, AA451735, AA973548, H19041, AW129980, BF791539, AW472838, H65681, AA478196, AA666224, BF940460, AI002830, AI374721, AI264277, H29405, BE930289, AA446666, R52737, N99048, F06358, AA233772, H11875, H65682, BF725919, R64291, R59440, AA812450, Z44951, BF825554, BE711465, F07390, AA093749, AI080343, R24935, R64256, AA878276, BF248328, AA081567, AA081513, R20695, D11945, AA249453, AW630557, AA331924, F07956, AI672272, AA383930, AA385881, R63983, AA865796, AI078076, AW964475, AA448551, BF878091, BF091153, T97552, AA453075, BE937893,

					N98627, T53666, BF836787, R64175, R63901, AA319203, AA424168, BF791814, BG001790, H11513, BF376043, W30696, BE739183, BF086020, BF376012, AW189731, BF769066, AA383577, AW388471, AW388477, AW810765, AW388507, BF247577, AW810647, AW810736, AA092943, T97598, AW810677, AW627523, AW810964, AI261898, BF216270, BF855391, AW810687, AI221448, AI147974, AI611624, AA730133, AI377784, AI672529, BE551587, AI936568, BF115500, BE466653, AW303619, AW388498, BF382656, BF751597, AI962331, AW006254, AL1351767, AI655026, AA884783, AL119457, AL119324, AL134524, AW971745, BE161864, AW149892, AL119396, AL119443, AW804686, AW392670, AF212247, AC007533, AX030435, AJ251859, AX046357, AB026436, AR060234, AR080280, AR069079, A81671, AR054110, AR066494, and AJ279014.
HCEJG71	36	715592	1 - 2221	15 - 2235	AL516212, AL516213, BE277026, BE874995, BG254851, BF337522, BE782438, AW957186, BE908068, BG111021, BE313308, BE304728, BE791759, BG165174, BE276912, BE294077, BE390036, AI608789, BE387937, BE391028, AW845399, BG036397, BF593816, AW952842, BG032631, AA411541, AW150272, BE389434, AI991149, BF939786, BF205750, BF725012, AW962210, AW473868, AI934755, AI763268, AI090866, AA464314, AI277953, AI624414, AW514028, AI954973, BE908223, AI167471, BE390099, W96217, BG027342, AI675874, AA604659,

					AW501761, W93790, AW016493, AA813712, AW082293, AV746836, AI159950, AI038163, AW957189, AA834939, BF766716, AI279359, AW845401, BE700939, AA297727, AW004853, AA297726, AA550765, H91883, AA456486, W96311, BE818916, T16058, BE772045, T36190, AA412342, AA382771, AA412452, AA781072, AA377166, AA344749, Z38920, AA369026, AA326408, AA341054, R41523, AI435982, AW016126, R18534, AA477934, AA664345, AI144001, AA722624, AA628669, W93789, Z42768, D45660, BF095971, T52089, BE777658, BE714008, H06991, BE844048, AL080162, AF097484, AF056183, AK000536, AC005089, AF097485, AK026529, AF097523, AC005089, and AC005089.
HELHL48	37	696945	1 - 2957	15 - 2971	AL529435, AL524123, AL524122, BF312538, AU129727, BG164871, BF348048, AU120482, BG167168, BE733600, BE876571, BE875645, BE296592, BE901138, BF343028, BF308771, BF345199, BF308189, BE336871, BG028125, BF115264, BG116986, BG249650, BE903726, AV728373, AW007132, BG121227, BF206051, AW963600, BF347698, AU151806, BE294229, AW303548, AW411067, AW967356, AW411066, AU128086, AA100522, AI867409, AU137055, AI378902, W28880, AW752755, BF308950, AW751506, AI421175, BG180673, AW590377, BF001722, AI872412, BF924126, AA180518, AI373035, AW179322, AI401197, R24305, AW178945, AW150193, AA209515, AA564224, AI370802, AI984047, BF438508, AA293441,

				AA088551, AI758667, AI275100, AW996404, AW007984, AI800710, AU150189, AI361596, AU150403, AA669849, BF432420, AI559326, AU146534, AA514455, AW513096, N31325, BF754347, AW896670, BE789836, AI299591, AI272929, AI089779, BE008621, AI912569, AI276235, AI283742, BF939706, AA508685, AA180517, AW169281, AI688823, AI310354, AW007978, AI359948, AA148446, AA292742, AA478976, AI041725, BE790438, AA292741, AI221864, AA157827, AA552023, AA112746, AA513477, AA232508, AA148445, AI493536, BE206110, N26490, BE147464, AA293508, T84545, BE093924, BF884193, AU157002, F12444, AI348568, D31225, N47540, AI269318, BE147790, AA088385, T74066, AA053180, H30187, AA654655, BF154572, AW579667, T88004, T35342, AI074255, AW571550, BG055222, AW579684, Z39831, BF434566, AW390755, AV698355, Z43770, AV685886, BE463536, AW270979, AW378596, AW514887, T31997, AA863225, BE296813, H04167, AI246176, AA365514, AA513359, AA477913, T34879, BF347090, BF438580, AA151938, AV684774, AA336395, AA492462, AW009840, AA053627, BF906710, T87910, AI470954, BF814719, BF593969, T64888, AA136495, AA179793, H08606, AA907036, F10066, AA503814, R22025, AW577064, BF749344, AA298224, AA339096, AA079476, T35287, AA936508, AI620090, AA079475, AW378971, T39180, F08643, H08605, AA372556, AA995437, BE294737, AW300420, AA496416, R01535, BE311798,

					AA345134, R44902, R22078, F02150, R49987, BE840622, T35182, AA369833, AI244019, BF947140, R00876, BE840609, BE294732, H04166, AA887342, BE143234, N47539, AW374684, T31964, AW178632, AA635427, AA188708, AW582129, R47850, AA152055, BF476766, AW291610, AA369871, AW451289, BE467357, AI630981, AW134630, BE763447, AI383035, BG255592, T58576, AA248989, AK001112, AL161962, AK001524, AF151847, AK001424, AL034405, T58537, and AA232607.
HISAQ04	38	589960	1 - 1149	15 - 1163	AV694051, BG178802, AV700042, AI635871, AW105519, AV763026, AV763058, AW502949, AI568849, AI368745, AI049709, AI090377, BG029528, AW962006, AA551390, AI683131, AW151541, AA525331, BF673854, AL079734, AV738383, BF821955, AA598443, AW275432, AV761486, AA515728, AA502532, AA831426, AV764383, AI804519, AI912401, AV759632, AI821467, AA736557, AW973992, AW833047, AL022324, AC003982, AL359382, AC016637, AL160313, AC011495, AC005695, AC009004, AL022327, AC005089, AL031281, AF109907, Z85987, AC004644, Z86090, AL138787, AL139095, AC003029, AC004596, AL049795, AC005081, AL035461, AC006111, AJ295844, AP000553, AL161646, AL139343, AC003002, Z84480, AL022326, AL034548, AL121753, AC004846, AC006536, AC008521, AL359828, AC005726, AC004590, AC005004,

				AC011465, AC004531, AC009228, AC012076, Z82172, AP001207, AC024239, AL159997, AP000544, AC015968, AL133163, AC006530, AL121751, AL035455, U62293, AL391684, AC005064, U63721, AL021391, AC011479, AL021937, AC004583, AC004542, AC008474, AC009403, AC008543, AF111168, AC004983, AC022206, AL137853, AL079340, AL031589, AL132773, AC005378, AC020550, AL021394, AL138725, AC002302, AL031295, AC008623, AL135978, AC011510, AC073316, AP002085, AL133453, AC016543, AC011484, AC005620, AC009333, AL121601, AC004890, AC004938, AL158040, AL158841, AC006160, AC004797, AL049829, AL034372, AC005280, Z98036, AC010363, AC011811, AL118501, AP001717, Z99716, AC003043, AL023553, AC004674, AC004224, AC007919, AC027319, AC020913, Z98742, U47924, AL049761, AL022313, AD000813, AC005512, AL030998, AC004685, AF305941, AL358777, AC004840, AC016898, AC002365, AC005480, AL136139, AL031311, AC004921, AC005274, L40817, AP001679, AC004383, AC006023, Z93023, AC020904, AL136418, AC006251, AL050309, AL031431, AC002425, AC007384, AC005049, AC006449, AF001548, AC005052, AL022323, AC007029, AC008764, AC004447, AL139100, AL137783, AC004824, AC005531, AC020552, AC004854, AL033529, AC005091, D83989, AC009464, U07562,

						AC004777, AC005874, AF134471, AL137100, AC009516, AC007954, AC006312, AL136097, AL021918, AL049780, Z85996, AC009892, AC005701, AL357497, AC005924, AC011500, AC007200, Z98044, AL137012, AC005778, AJ400877, AC021863, AL121890, AC011444, AP000244, AC005058, AL035699, AP002898, AC008687, AL121774, AP001694, AL160231, AC020916, AC009314, AC005913, AC011462, AL031005, AC004000, AC004876, AC087094, Z97989, AC009244, AC007739, AL031727, AC018644, AC004922, AL109935, AC000085, AL137797, AL136304, AL080243, AC005484, AC005921, AJ251973, AL133244, AL121891, AL096712, AL136109, U91323, AL163279, AC008685, AC017006, AC005566, AL022324, AL022324, and AL022324.
HJACB89	39	689899	1 - 1918	15 - 1932		BE902912, BE902594, BG105130, BE908526, BG113157, AW361313, BE328831, AL040909, BF130137, AW043726, AI871093, W94722, AI654017, AI857485, AA609172, AI610359, AW019869, AA922082, AI363492, AA833529, R35261, AA737909, AA826460, AI497959, BF881634, W24732, AA039350, BF248109, AI536808, R50932, AA039240, AA331160, AI686320, AA310841, N57831, AW088881, AA588757, AI364550, BE902668, AI685789, AA337988, BF090955, BF109505, AI184432, AI914850, AI217275, AI468096, AW401412, BG001512, BE936756, AC019054, and AC013356.
HTECC05	40	666743	1 - 867	15 - 881		AI040972, AI806582, AA437009, AA442839, AA759268, AI214390, AI799076, AA918443,

HBJLF01	41	732111	1 - 1918	15 - 1932	AW195596, AA910234, and AC040950.
					BG261130, BG121213, BF347966, BF796462, BE899286, R17115, AI123525, AI697325, BE783654, AW402585, AA032055, BF724098, AA031919, AW402594, AW402872, AW026287, W89010, AI926967, W95778, BF887406, AI376419, BF381332, BF507805, BF888120, AA233002, AI669291, AI963299, BF744292, BF907549, BF907541, AA954836, BF888127, AI768850, AA768759, BF888128, AA232951, BF744299, AW090314, AI571824, BF888074, N73038, AA480645, N53675, AA886377, BF888119, AA535561, AI864506, BF799491, AI217778, N51612, BF381336, N53906, BE819619, AI806785, BF744934, W95735, BG251027, BF381311, AI674508, AA016130, AA743705, AA917873, AA649797, BF887394, AA631017, BF907590, AI480218, AW302053, BE139664, Z39059, H86222, AA954334, AA456896, AI244571, AA015836, AI341715, AA485019, AI078627, AI015866, AA827439, BF745018, AW271993, AA954612, AW001670, AK000208, and AC083866.
HBXGP60	42	566892	1 - 1150	15 - 1164	BF671784, BE536052, AI913628, AU149885, AI680075, AW054875, BF512779, BF509344, AI373323, AW473443, AI953258, AW662614, BF038439, AI565458, AI651053, AA643721, AI224511, AI950680, H16805, F02963, AI697019, AI698350, AI934370, AW007591, AI700400, AA992991, AI917570, H16915, BF447312, AI912227, AA601933, BE019300, F03939, R93327, BE774158, T09346, BE563281, T09490, BE161378, BE161373, AK001383, AB046846,

HCE5B20	43	544507	1 - 1091	15 - 1105		AC026942, and AC026942. AW275464, AW079718, AW275556, AC025779, and AC018883.
HCMSQ56	44	740781	1 - 1248	15 - 1262		AI243049, AA778231, and AI248811.
HCNAH57	45	694610	1 - 503	15 - 517		AA327204, BF764474, BF764476, AW847311, AW847327, AW847328, AW847319, AA613739, AW022897, AA548890, AA433996, AA284871, BF676981, AI267161, AV705299, BF874758, AI369580, AI254913, AA659232, AI311684, AL042853, AW843301, AL134242, AA766310, AW963750, AI433008, BG029528, BG222337, AV756491, BG222576, AW369785, AA219018, AI873990, AA478355, BE907585, AW084246, BG115537, BF974349, BE175939, BF347740, BF347791, AI311234, BF030591, BF343686, AA449997, AW303196, AA584733, BE154678, BF874773, BF854223, BF675251, AA719292, AI924948, BF965290, AI673336, AA577824, AW858127, BE277210, AA631517, AW022655, AV711465, BE276480, BF725029, AI343233, AI249880, BF846505, AA469400, AA100718, AV701507, AA601202, AW301350, AL038606, BE159616, AV733830, AA601125, BF857083, AI732677, AI732710, AA584125, BE066105, AA167055, AA279421, BE066002, AW796784, AV764255, BE409047, AV733029, BF342223, AL048135, BF828577, BE902562, BF337291, AC006333, U82670, AP001672, AC087225, AC005999, AC004552, AL161663, AF042091, AC020750, AL096699, AL163282, AC018833,

				AC010223, AC087092, AL355916, AP001671, AJ400877, AL162414, AL121601, AC022404, AC011450, AC002404, AC004972, AL161804, AL021026, AL035423, AC009086, AC008474, AC018764, AP001675, AL159977, AC007919, AC008162, AL121657, AF117829, AL163201, AC008739, AL031681, AC007253, AL352979, Z76735, AL022574, AB020862, AC006464, AL390738, AL137016, AL133480, AC026881, AC008738, D84394, AL096770, AP001666, AC002464, AC007040, AC027644, AL031311, AC010201, AF088219, Z98046, AC008008, AP001607, AC004895, Z95114, AC006039, AL356108, AL353700, AC009530, AC005341, AC004933, AL138956, AC007486, AF067844, AL353573, AL357752, Z95126, AC009481, AP002529, AL391354, Z93019, AC006028, AC007021, AC004066, AL360227, AC020550, AL049629, AL031274, AC008892, AC062020, AC004675, AC005000, Z94801, AC024167, AC004087, AC006525, AC005670, AL391259, AP001669, AC003950, AC007097, AC006121, AL135926, AL121774, AL135932, AC004159, AL049641, AL008629, AC005680, AL391595, AC002407, AL136418, AC002457, AC000119, AC022596, AF111167, AC005820, AC009155, AL160231, AC023798, AC003029, AC008772, AP001699, AC023511, AC005216, AC007312, AC010200, AC008115, AC006374, AC005028, AL161905, AL135936, AL354653, AC004125,

HCUEP91	46	610610	1 - 844	15 - 858	AC009247, and AC022432.
HDPCJ91	47	740748	1 - 6093	15 - 6107	AU119059, AW959367, BF792861, BF672087, BE439439, BE717153, BE770928, BE718895, AW971539, AL079949, BE770941, BF687684, BF132755, BF727151, BG009815, AI703121, AI066742, BE968461, BE717019, AW444843, W61007, AI949993, AW502324, AI150343, AI859085, AA393478, AW467411, BF515251, BF063545, BE717046, BE042969, BE673935, AU154204, AA292253, AA838717, AU145486, AI273190, AW512776, BF727150, AI084372, AI597583, AI457829, H99255, AW474793, BE327577, AI697937, AI167388, AI684736, W69563, W31042, AW753588, N98496, AI307397, AW613687, AW241267, BF198110, W60918, AA291214, AW316965, BF090819, AA988341, AA908177, AA043254, AA651802, AA502341, BE536255, AA043612, BF431421, AI261626, BF214133, AA972952, AI334810, R80993, AI539739, D62886, AI611313, N28297, H99484, AI825223, AW938439, T65655, AI221607, AA169878, AA435697, AA262010, W69419, F11961, T34633, AI873428, AI457907, BF103809, T65584, AI695552, AA126467, AA641749, AW882312, N52582, BG1499944, BE669976, D57676, AA169566, AA126647, F09610, AA446424, R78978, AA291524, D62733, T15751, AA169579, AA628830, AI796712, C18687, AA649257, AI431924, BE763704, AW374026, AV746759, AA091017, R13144, D79785, BF589508, R40624, R78884, AA250810, T20017,

				AA747613, BF725884, BF806370, AI733856, BF832074, AI635440, BF827469, AW504299, AI683131, AI291823, AI732789, AA236703, AI251034, AI355587, BE139139, AI336054, AI312790, AI250552, AW963463, BG222875, AI039809, AI223626, BF725844, AI284543, AI251284, AI251203, AW268329, AI254770, AA602906, AW673941, AV764259, AV647070, AI569086, AW303098, AA524800, AI249886, AI251241, AW474921, AV737641, BE042006, AI082510, AW971342, AW088049, AW068007, AK001067, AX018002, AX017863, AF162853, AC007688, AP001718, AL163281, AC009134, AL117336, AL359382, AL121890, AC007540, AC008651, AL031388, AC006013, AC018764, AC005747, AC002072, AC007792, Z82203, AC004593, AC068799, AL121656, AF020503, Z83822, AC005874, AF134471, AC004752, AL023575, AC006021, AC004638, AL161670, AL117377, AL050335, AC002287, AL139187, AL137061, AL031132, AP001726, AC007225, AC004953, AL137783, AP000696, AP001712, AC019187, AL355365, AL021395, AP001706, AL031273, AC017100, AP001694, AC020917, AC007639, AC009333, AC015541, AC005538, Z82244, Z83845, AC016831, AC009505, AC004949, AC004965, AC005358, AC007388, AC007462, AC006483, AL356244, AC002368, AC026162, AC020741, AL096814, AL390755, AC005514, AC008474, AC007151, AC008066, AC004032, AL034405, AL442064, AC019046,

				AC006115, AL138725, AL163209, AP001705, AL138755, AC003950, AC011331, AC002367, AC022308, AL137780, AL035415, AL035697, AP001729, AP001674, AL034549, AF134726, AF130342, AL163249, AC004905, AC004891, AC008812, AC005274, AL133255, AC010271, Z83826, AC006211, AL031228, AF001549, AC003012, AC004383, AL354680, AC004913, AC009263, AC002476, Z97353, AL445472, AC008738, AP000014, AC016673, AC005803, AC022336, AL158206, AC006430, AC006345, AC011464, AC016716, AC005703, AF168787, AP000563, AP001688, AC004885, AP001619, AP000236, AC005939, AL133355, AC012000, AL133387, AP001666, AF124730, AC012502, AC002365, AL133391, AC006120, AL138997, AL133215, AB023048, AC005988, AL360078, AC018731, AC009044, AL138836, AL031846, Z73417, AL133551, AC010722, AC004673, AC006288, AC004491, AL136979, AL022334, AL031658, AL031776, AL445189, AC006239, AC006334, AC002565, AC004382, AC009518, AC022206, AC020906, AC002331, AC006327, AF243527, AL157818, AC007542, AC006450, AF064858, AC002299, AC005751, AL022329, AP000697, AL121653, AC003670, AC008551, AC006333, AC017002, AC002073, AL133246, AC069298, AJ229041, AC004605, AL023807, AL121754, Z97055, AC005821, AL161938, AL163303, AC006960, AC005146, Z77249, AC007685, AL138976,

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HDPGK25	48	704067	1 - 689	15 - 703	AW976171, BG258661, AA427627, AA811193, AI275905, H20137, AI384044, AI339568, AI739227, AI923644, AI970737, H39189, H45408, AW130654, BF059008, AI659951, AI739226, AI142039, AI394459, AA968938, AI269770, AI392978, AA969916, AI364323, AI378436, AW137018, H46909, AW615186, AI356177, BE747585, BE898748, AA714852, AI934509, BF763404, AV745344, AI000835, BF877861, and AK025886.
HE2DY70	49	722217	1 - 625	15 - 639	AI983739, AI093491, BE464707, AA169811, AA232650, AA609946, AW023590, AW163464, BG260037, AW087445, AL515047, BE785868, BF680131, BE045182, BG257535, AI344817, AV712673, AW071417, BG179993, BG110517, AI345746, AI251205, AA830821, AV725055, BF726237, BF342070, BF792961, AI308032, BF344652, AL514129, AV711509, AV715560, AI802542, BE964614, AL079963, BG163618, BF726183, AI969641, BF970731, BG164371, BE910703, BF037097, BG104782, AW827289, AW103371, AL120853, AL110306, BF885081, AI929108, BE964876, AI815855, BF904180, BF856052, BE965432, BF792469, AI340603, AL514529, AL514357, BG035511, AI521012, AL036802, AI344785, AV681719, AI590120, BE966443,

				AW935969, BF793309, AV682051, BE047852, BE620084, AI620517, BF341801, BF969494, AA225339, AI909666, AL043981, AL037454, BG109221, BG109270, BE874133, BG110684, BG120816, BF904258, AA427700, BE018334, AV654624, AV764282, BE965014, BG036846, BE048071, AI364788, BE789764, AI619502, BE964497, BF816811, AV706744, BF970768, AV703585, AL119863, BF526407, BF037484, AV660662, AI537677, BG168549, AW082594, BG180996, AI627880, AI471361, AV764180, AL080046, AI569583, AI400725, AW999049, BG261093, BF526020, BG121222, BF133418, AW026882, AI866741, AI536685, BF527014, BF812938, AL036804, AV682289, AI623682, AW268220, AV714485, BE964593, AI349645, BE905394, BE619280, AI433976, AL119791, AV686346, AI497733, AI433157, BE964460, AI619716, AW167222, AI702073, BF910810, BG180046, AV764059, BF812961, BF812960, AA640779, BF344691, AW978080, BG179633, AI348897, AL045500, AI699865, AA572758, BE964636, BG114104, BF921291, AW075305, AI612913, AL041772, AL513943, BE965621, AI340519, BG058398, AI921248, BE965481, BE904902, BE891101, AL121270, AI922901, AI282326, BF904265, BG249582, BG252914, BG105099, BF885675, AI783504, AA814407, BE879906, AI620284, AV681647, AI358701, BE965067, BG168185, AW087901, AW238730, BG168696, AV733470, AL036274, AL041150, BG109857, BG114432, AW827103, BF753056, F37471, BE963035,

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HE2NV57	50	740750	1 - 853	15 - 867	C05927, R72949, AA327984, AC016673, AC001929, AC058786, AC016716, AC008066, AC003969, AC024082, AC002302, AC013246, AC011490, AL158064, Z98743, AC020610, AF195953, AC016910, AF110520, AL359394, AC005227, AC003692, AC002300, AL157838, AL031737, AL050335, AC007690, AF220294, AC004541, AL022401, AL008583, AC005868, AL133383, AC006070, AC006211, AC012526, AC009424, AL391686, AP001684, AC006013, AL158817, AL035685, AC006134, AC020906, AC015983, AF188024, AL357519, AC005081, AC005886, AB020875, AJ011930, AL163300, AP000952, AL133387, AP000953, AC025765, AC004891, AC003060, AL355792, AL163280, AL109662, AC010206, AC012302, AL049843, AC009362, AC005015, AL096791, AC007942, AC002487, AC005835, AC010726, AC005344, AC022363, AC009498, AP001699, AC008064, AL357507, AP001670, AC012147, AL137061, AC004585,

						AC004963, AL445243, AL109618, Z97195, AC005146, AC007151, AF130342, AL138976, AL023513, and AX015907.
HETBR16	51	703243	1 - 1555	15 - 1569		AW661837, AA127395, D62246, BF838051, AA363498, BF673053, BF838050, N68223, AA608520, BF878696, AW238127, AA570224, AI635819, W45298, AW949001, BF932686, BE063025, W45283, BE063030, BF815072, F31654, AI610607, AI640411, AA568947, BE049229, BF856556, AI679442, AI679952, BF857619, AA665645, AV656064, AW949012, AA653612, F27410, AV740009, AI889440, AI540408, AV720211, BF850690, AA605266, BF844769, AW261996, AI885488, AA494090, AA626402, AW020088, AA486970, AW167154, AI809818, AA745356, AI634601, BE162124, AW271917, BE179216, AI859280, AU158549, AW148386, AW971243, BE674880, AA661948, AA665330, AA649148, D82461, F31619, AI565245, AI932902, AA708213, AL021807, AL132718, AL132653, AP001417, AP000160, AL122023, AP000018, AC008122, AP001730, AL078475, AL050302, AC006026, AC004964, AC008745, AL163203, AC002115, AL118524, AC004098, AC006387, AL033529, AL163210, AC011455, Z98048, AC007637, AL021408, AC021019, AC005668, AC011497, AC010150, U85195, AL135839, AL445490, AL033378, AF258547, AE000658, AL133545, AL031666, AC011540, AC002350, AC007881, AC007954, AC022407, AP001746, AB020878, AC007055, AC003029, AL158089,

					AL391384, AL352979, X87344, AL445466, AC083875, AL161938, AF084941, AL008723, AC011604, AL359238, AC018448, AC004066, AC068948, AL035671, AL050335, AC003954, AC010620, AC021016, AC005666, AL135927, AC007227, AC008636, AC008521, AL022717, AC019171, AL356782, AC003106, AL034349, AL035587, AC007263, AC010422, AC004671, AC005899, AC005406, AC004686, AF008243, Z94801, AL031734, AF015416, AL158040, AL354993, AC005670, AL121891, AC005000, AC005971, AL137230, AC009086, AL137853, AC006211, AC002985, AC005209, AL445196, AL109946, AC011494, AC006500, AC015968, AC006353, Z85999, AC006017, AC018832, AC005399, AC010267, U80017, AC005411, AC000385, AC003041, AC011479, Z97630, AC004881, AC008770, AF111168, AL133406, AL139188, AC008733, AL357519, AP001624, AC010326, AC006050, AC005479, AL136969, AC010598, AC008831, AC027319, AL022320, AC024561, AC020906, AP001728, AL121886, AL035361, Z99128, AL031681, AC007057, AL049872, AC004491, AL031662, AC005324, AC004859, AL357150, AP001732, AC006045, AC022137, AL049840, AP001037, AC010457, AC069254, AC069254, AC021617, and AC021617.
HFXDG13	52	657390	1 - 1182	15 - 1196	BF338151, BG120864, BF869369, AW893984, AV649111, AW967373, AV648643, AV731739, BE063143,

					AV732052, BE150807, BF875669, AW964353, AA847690, AW992839, AW391396, AA931987, AV648844, BE169205, AW969095, AI026925, AA831680, BF749712, AW975190, AW207719, BF433821, BF883025, BE065321, AI860789, AI198511, AL120314, AA595827, AA205322, AA147639, BE972284, AU156961, BF951370, N29555, BE674204, AI114511, AA565909, AA504616, AW896115, AA632808, BF735857, AA435704, BE080185, BF223671, AA613886, BF923208, AI805822, AI080461, AA398802, AW962969, AI660010, AA847407, BF110238, BE083044, BE644710, AC021058, AK001116, AL024507, AC023480, AC024167, AP002023, AL158050, AL117339, AL163210, AF235093, AL356098, AC016673, AC005399, AC007317, AL122057, AL049821, AC011310, AF280107, AC004026, AL109662, AC002385, AL023875, AL161666, AC010395, AC027329, AC007444, AL133417, AC010202, AC022268, AL022401, AL034347, AC004745, AC003686, AL022144, AC061958, AC009332, AC009264, AC074191, AL023713, AL121757, AL031772, AC083875, AC006120, AC079844, AL035427, AC018360, AC005019, AC004051, AC006479, AL133214, AC002454, AL355345, AC009301, AC002065, AL353667, AC011088, AC004823, AL035661, AC024094, AL354750, AL157830, AL356022, AC017004, AL355871, AL035089, AJ271735, AL445068, AC073539, AC006239,

					AL136295, AL096801, AP002531, AB042235, AF002997, AC020550, AL035397, AL136296, AL138900, AL109800, AC000119, AL136520, AL035695, AL360272, AL135936, AL135902, AL359846, AC003106, AC004083, AP001671, AC010176, AC000125, AC010369, AL109761, AL109764, AF013593, AC007239, AP000379, AF088219, AL353788, AL355390, AL157384, AL132639, AL031116, AC005050, AL035401, AF235098, AC009506, AC007567, AL161743, AL157791, AL356115, AC009232, AL021307, AC068770, AC005588, U82828, AL356057, AL139123, AC009480, AC012611, AL079303, AL022345, AL353582, Z82899, AL354977, AC008407, AC005101, AL137026, AC009405, AC005176, AC004842, AL117191, AL035262, Z68871, AC005201, AC000389, AL133284, AC004931, AL121652, AC016689, AL133325, AC004010, AL136308, AL357153, AP001346, AC005191, AF241733, AF282856, AL121927, AL138702, AL391666, AL158832, AL356244, AL121582, AC078937, AL031599, AC007090, AC073323, AC002357, AC019183, AL121694, AC009517, AC012558, AC021070, AL121977, AC008070, AC024576, AC006265, AC002079, AC007690, AF188025, AF196972, AC008430, AP001674, AP001538, AF245226, AC007158, AC005509, AL096800, AC069313, AC008174, AC022224, AC006427, AL132774, AC003687, AC016716, Z71182, and AL109942.
HFXKY27	53	634161	1 - 931	15 - 945	AA483223, AA552843, AV762050, BF991286, AA623002, BF827410,

				AW193265, AI434706, AV759204, BE350475, AI270117, AV760937, BF217299, AV710066, AA610493, AI350211, AL041690, BF475381, AV764241, AV764307, AW673241, AV762139, AI192631, AA552856, AV763540, BF676536, AA468131, AV682003, AI368256, AI345157, AA649705, AI345518, AV760774, AA480772, AA521323, AI538433, AA644538, AL037683, AA577906, AA613227, AA503475, AW270382, AI355206, AW021583, AV759274, AA521399, AV761155, AA492166, AV735495, AI431303, AA490183, AW088846, AF330238, AA857486, AA493621, AV759382, AW438643, AA579362, AI610159, AA525790, AA507824, AV742057, AV763255, W60061, AV761786, AA644551, AI254615, AV735370, AW872676, AA649642, AA652057, AA984708, AA579736, AA682912, AA525824, AW238583, AW977303, AA470969, AI963720, AV734666, AV760624, AV762826, AA970213, AA908422, AI613280, BG150790, AV760777, AA834755, AW513362, BF668217, AA657535, AV761925, AA357937, AV730301, AV763971, AA491831, AI688846, AW731867, BE502107, AW517737, AV762558, AW238542, AA766151, AA862173, AA350859, AI619997, AA501418, AV702857, AA601355, AI634384, AF001552, AL122015, AL034405, AL035699, AL365315, AC010269, AL022163, AL031661, AC005084, D83989, X55926, X54181, U57007, X54178, U18391, U18392, U57006,

				U18394, X55925, U57005, X54179, I51997, X75335, X55932, AC020728, U18390, AC004887, M37551, X54175, U57009, U18395, AC006511, U18393, X54176, U57008, AC005521, AC004662, AC004525, X55923, AL136090, Z22650, X54177, AL133332, AP001677, U18400, AC009481, U18396, AL121891, U18399, U57004, AP001696, AC002529, AC005740, AL049745, AC006287, AC009498, AC008168, AC004972, AL031275, AL139350, AL050325, AC005913, AC010748, AL132777, AL109755, AL157830, AC002303, AC009508, L47228, Z77249, AP000501, AC006376, AL049563, X55927, U18398, AC005274, U18387, AL049539, AL138721, X55930, AL023281, AC009802, AC027345, AC002115, AC007272, AC008109, AL355578, AC018637, AL049713, AC004622, AP001700, AC005158, AF117829, AL132639, AL163278, X74558, AC007934, U67831, AC022335, AC022407, AL133415, AC008134, AL354751, AC011310, AC005544, AC005297, AC003010, AC004491, AC002128, AC009311, AP001727, AL163248, AL359012, AL022162, AJ011930, AL050333, AC002091, AJ006995, AC006128, AP002532, AC007970, AP000555, AL138759, AC012315, AC007179, AF149773, AL049613, AC008071, AC007132, Z72001, AC004806, AL133344, AF195953, AC004865, Z92844, AC004047, AC006375, AL133472, AL031390, AC008268, AP001683, AC008482, AC003983, AC017004, U67829, AL109823, AD000090, AP000472, AP002026, AC016716,

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HHPEC09	54	695726	1 - 474	15 - 488		
HISAD54	55	740754	1 - 2846	15 - 2860		BE387604, BE386701, AW138815, AW170555, AA402189, AW964645, AA402043, AA426655, AA402659, H08552, AW025318, AI275121, AI760500, H09223, AW204890, AA132741, AI362705, H08551, AA631662, BF431834, H09165, R69556, BF379963, R85615, AA132648, AA402676, BE549179, H52666, R69424, AW779499, AI869911, H52667, AI557584, AA322657, T09320, BF756532, R58145, AL136293, AL136293, and AL136293.
HJBCY35	56	719729	1 - 1545	15 - 1559		AL518865, AL526445, AL518864, BF690211, BE795952, BG261247, BG122941, BE871131, BF342499, BF797882, BG034854, BE874386,

				BF684303, AW958340, BF055513, BE265238, BF055496, AL042954, AL044311, AW393087, BF590235, BE251517, BF688851, AW500006, BF750912, BF436031, BE207255, AI523943, AI809559, AW615714, AI088845, AI199469, AI088821, BE792741, AA707004, AI393362, AI859578, AA864359, AI359119, AI963339, AA259086, AW027379, AA186786, AA703021, AA305929, AA393356, BE729570, AI961726, AW274049, AI216448, AW503180, AW505339, AI015694, AA291342, AI049539, AW873566, AI092749, BE410341, AI817912, AI870620, H44330, AI366215, AA258242, R46300, R16949, AI744596, R54656, BE386449, BE410337, AI807057, AW081887, AL041401, H15972, BE710574, BE410414, BE535502, BE222788, AA398688, AW273864, AA404987, D59795, AA077661, BE047327, T10451, AI871075, D59810, AI368575, BF526818, AA962247, AA335735, AW000813, BF435172, AA188015, R75708, AA329264, BE713106, AI218840, AA329538, AA291343, AA826970, T35806, R10855, D59833, D59821, BE547124, D80231, AI080034, AA299767, BF203222, AI908002, AA973311, AW087244, BF920764, AI648592, D80329, BE537114, BF511965, D59677, W93021, AI919083, AA749327, R16895, R55419, AA354448, AA136776, R54853, R46205, D59561, AI969256, W51754, AW273865, R10856, AI452772, BF765954, R10335, BF858687, AA076725, BF955782, BF206768, BF310354, BF032473, C01203, AL050110, AB037861, and AL137358.

HKAEA19	57	721489	1 - 2050	15 - 2064	AU120021, BF982844, BG169037, BG034578, BF036852, BG257906, BF568991, BF034397, BF905903, BE873247, BE893899, BE871129, AW957258, BG171337, BF036222, AA746226, AA573750, BF241654, AA236296, AW161827, AU150270, AA100812, AI809272, BF572758, AV713641, AI814417, AA600756, AI435028, BF679650, AI952058, BG253263, BE565828, AI669150, BE565013, AW471028, BF439102, BF569093, AA812943, AU128660, AU157320, AI300864, AW026387, BF906228, AI459100, AW072665, AW007290, AI346638, AA664274, AW157692, AI499354, AU151173, AA126954, W94441, AI984523, AI243221, AW243843, AA127163, AW157153, AI686902, AA903712, AI301646, BE746831, AU135873, AA877280, BF905975, BF185758, AI377065, AI680057, AA721330, AA194102, AW084970, AI022296, AA693624, AI538995, T82203, AA722895, AI803272, AI827881, AU137800, AA219348, AI244836, BF855557, T57283, R53227, AU131888, AI445306, R85862, R84465, AA455731, AA447739, AI808020, AI079234, AI240429, AI270490, AA683509, BF196711, AW135701, AV654872, AA172009, BE280022, R52411, AU130432, BE875994, AI758507, BE870395, AW135133, BF568465, AW340772, BE311979, R53228, AA236230, BE893096, T90533, AW163123, AI282353, BF568684, AI364022, BF513976, BE928347, AA504085, BE780164, BF206624, AW339342, BE698049, AW467264, AA370946, AW967026, AA306000, R34900,

					AI903187, R87773, AA931878, AI627596, T56598, AI632989, BF316539, T82202, AW207618, R49289, AA328743, AA453671, T83068, AW376775, BE312569, BF983061, N23184, AU146213, AI873742, F02007, AW376774, BE898186, BF818799, BF905385, Z38683, BG030212, AL047822, Z42488, W94256, U25896, AI694590, AW892280, AI376246, AW161261, AA081761, AW161371, AA081750, BF893952, F05758, AU152388, BF905361, BF905369, BF906220, BF808687, BF905827, BF905829, BF905826, BF906173, AI769338, BF366557, BF366575, BF908288, BF366406, BF366419, BF366620, AW947032, BF366436, BF366548, BF366507, BF366535, BF366659, BF366625, BE766445, BF366593, BF366600, BF366545, BF366657, BF366481, BF366415, BF908287, AW192397, AW059667, AK023085, AK002031, and AB032470.
HKGDL36	58	704088	1 - 1036	15 - 1050	BF966686, BF969262, BE798423, BE383172, BG108317, BF438085, BF967072, BF724971, BF437374, BF525713, BE327726, BF725537, BF983368, BE045542, AI261620, AI628667, AI955247, BF966496, AI796185, AW024651, BE392518, AI365220, AI767645, BE551437, AW051507, AI199503, AI418919, BF724666, BF310167, BF310234, BF724972, AI039610, AW162506, AW138191, AI955309, BE673721, AI969138, AW583447, AI373491, AI696987, AW583390, AI952012, AW341037, BF526596, AI758216, BF438130, AW013963, AI955147, BE669440, AI768473, D61105, BF592013, AI355910, AI969092, AI423438, AI968975, AI479582, AI913491,

				AW027769, AW090177, H41372, AI927970, AW300071, AI400855, AI348277, AW771649, AI672352, AI991536, AI421291, BF739771, AW103643, AA894790, BE312863, BF197448, BF197412, AW000953, AW299323, BF724667, AA199635, D59847, AV748923, AI560270, AI498193, AI625846, AI493832, AW590037, AW583609, AW955700, AI702136, AA877175, AA757536, AW583672, D59877, AA706516, AW393735, D60795, D80419, AI302316, AI248555, D80214, D80684, AI927667, AI627691, AA989221, BE464388, D59878, BE218723, BF346124, AI985164, AW000934, AW001692, AI701771, D59848, D59725, AA873392, AA364835, BF431598, H92678, AW135417, AI589246, AW072965, AI916619, BF752892, BE964512, AL515163, AW022102, AI783861, AL513839, AA600801, BE621073, BE544111, BF815196, BF910849, BE963809, BF814409, BE784387, BF840099, BE963918, BG170109, BE613727, BE880341, BF814360, AW005029, BF921092, AV712606, AV681927, BE967251, BE964621, AI866741, AW059713, BG108334, BE536377, BF929585, AI254754, BF764538, AA824513, AW083804, AI539462, BF129016, AI446605, AL513741, AA830821, BE966699, AI924035, AI445976, BE875966, AI242248, BE885353, BE538466, AI620093, AI537643, AI358042, BE880697, AI683255, AI591412, AI591081, W81248, AI536910, BE964962, AW834325, AI864827, BE048026, AI872159, BE061389, BE964767, AI591057, AW073868, AI863256, AI690449, BE907440, AI884574,

				F35927, BE878032, BE965121, N95566, AV743128, AV706465, AI445588, BE899377, AI934000, AI280670, AI583578, AI627714, AI500039, AV708075, BE900603, BF752858, AW265004, AI623682, BF341610, AW079032, AI925736, AI252077, AI590787, AW025533, AI267185, BG105895, AL513789, F26535, AL048377, BE965527, BE967255, BE964799, AW946864, AL514167, AI627880, BE621140, AV710267, AI678302, AI926878, BE878028, AI633300, BF817402, BF753053, BE875407, BF752999, AI689614, AI624668, BE966390, AI811192, AI866002, F28295, BG260275, BE963286, BF753056, AI686631, AF181562, AF196971, AF181560, AF293356, AF181561, AK000212, AJ012582, AF185576, AF113690, AX014095, AK024601, AK026865, AK025491, U77594, AF200416, M27260, L13297, AL137557, U90884, AK000598, AL121656, AK025906, AF194030, AJ010277, AL157464, X95876, I30339, I30334, AF155148, AL080162, AF026008, AK027113, AF036941, AK026600, AL137556, AF065135, AK026164, AK026613, AF077051, I48978, AF087943, AF028823, AF112208, AL137665, A08910, AB031064, A08909, AL137547, AR075041, AF218034, AB049629, I17544, A08908, AK026590, AK026603, AL049347, E15569, AL389978, AF116644, AL049460, X06146, S77771, E04257, AX019230, AF225424, X93495, AB047904, I00734, AF022813, Y16645, A65340, AL137459, E00617, E00717, E00778, AF111847, AL353935, AX019229, AR011880,

				AF266204, AF244915, AL359622, AL049314, AB047941, AK025119, AF205861, AF158248, AL133568, AB029065, AK000432, M92439, AF010191, AL117648, AL137657, AF069506, AF119894, AL133081, A08913, AL080137, M79462, AK025410, AL390167, A18777, I89931, AF119337, AK026533, Y16258, AF090934, Y16257, E02756, Y16256, E15582, M96857, AL162062, AL136842, A93016, AR087170, AB019565, AF031903, AK024594, E03671, AL122050, AF132676, AF166267, AX005848, AX005804, AF061836, U87620, AR059883, AF113676, AF217991, AL389935, I08319, AR038854, M84133, AF260436, AL353625, X66975, AK024570, AK000450, AB016226, AK024533, AB048888, U00763, AL133645, AL359596, AK026741, AL117585, AB044547, U96683, AK000310, AF036268, AB049758, AL080074, AL442082, U42766, X72387, AL049339, AK026086, AB047897, U53505, I26207, AK025239, AL359623, A08912, AF116610, AL110225, AL122118, AF321617, A08911, AC025226, AK026649, AF271350, U01145, AK026045, AK000652, AF151076, AF188698, AL133062, AK000445, A08916, AF089818, AL137648, AL157483, AK027142, AF130082, AK000323, AK025517, AX027129, AL353956, AL050092, AL096751, U91329, AF081197, AF081195, U49908, AK025383, A08907, AL080060, A07588, AB049849, AL162008, AK024538, E04233, AF119896, AB047887, AB047623, AK027081, AK027164, AL122098, AK000655, AK000421, S69510,

					AF130068, AL137284, AL049466, AL080148, S76508, AB034701, I89934, S78214, AK026591, AL137539, Y10655, AL122110, AK026542, AF130066, AF017437, AK027116, AL049300, AF097996, AL137298, AX046603, AL049283, AK026522, AF143723, AF118090, AL353957, AL122111, AL110197, AF110640, AK027146, U68233, I92592, AK025782, AF130077, I66342, AL133077, S79832, and AF196971.
HLDBS43	59	722228	1 - 2519	15 - 2533	BE622991, AW963656, BG119873, BE877983, BG165586, BE540985, BF799495, AW384813, AW303432, AW364609, AA806218, AW364624, BE350826, AW364630, AW341530, AW027611, AI805297, AI337288, BF515285, AA843910, BE880133, BF841931, AU151830, BE350822, AW273064, AW298520, AW190250, AW418697, AI342360, AI803510, N41607, N30632, AA424201, AA451978, AA769583, AI949818, N29607, AA054360, AI807818, AI291337, AI818369, AU149416, AI740886, BF792293, AW117975, AW090291, AU126858, AI625006, AA056298, AA056251, BF769886, BF928449, BF956332, AI962665, AW304814, AA282124, AA054279, N41848, BF907600, AA446752, N30604, AA001856, AA227696, AU150222, W81474, BF935958, AI189506, N66649, BE620497, BE965154, N30620, W02645, AI800851, BF111474, AW182011, AI829418, AA995105, AI271773, AA554274, BE762482, AI632180, AU149636, H70705, N39917, BE161874, H50951, BE762487, AW977059, W30945, AA995103, AW176652, N41877, AW384822, BF841753,

					AI167563, BF888788, R98741, AA909396, AI933933, BE762486, AW366588, AI468596, R98740, AI784629, AW888548, AA373411, AA432068, AW138399, H96404, AA760985, N27172, D81521, H70704, AW805828, C18685, AA424177, AW196470, T48542, AI918473, AI869870, Z19078, N29687, BF824815, AA366193, AA227557, C17395, T27525, R27150, AW819642, H51610, BF090148, AA705887, AW364641, AA478490, BE697462, R26908, AW364628, AW385624, AW860035, AA282125, AI799369, AA825692, F33903, BF326595, AA905767, BF931460, AW475022, BG009907, BF761670, AA187106, AA721174, AL137497, AF216644, AF225417, AF277625, AL133113, AK001338, and AC005046.
HLWAD92	60	695736	1 - 885	15 - 899	BF346613, AW084463, AW170356, AI762784, AI684513, AI992037, AI423926, BG116279, BE548119, BE857056, BF686616, BF112165, BG109119, W72376, AW960392, BG179066, AI149833, AW025395, AI660214, AA521138, BE045815, AI860646, AW190103, AI799279, AW469213, AA612928, AI079941, AI090661, AW150153, AI151095, AI147889, AI090989, AI991036, AI680208, AI279071, N90763, AI349504, AI122692, AI760878, AI160816, BE262067, AI141126, BF112061, AI252763, AI150238, AI042160, AI814304, W67964, AI936761, AI581187, AI042090, AA455783, AI140818, BE646616, AW149828, AI333625, AI955672, BE046116, AA398208, AI051058, AA481262, AI189920, AI808806, AI498841, AA776472,

				AA977692, AI926685, AA934728, AI266480, AI391679, N25910, AW473959, R85555, AI274499, BE502692, BE675866, AW954644, AI453811, AL043626, AI285057, AI200064, AA025402, AI061408, AI015608, W22174, AI200490, W72998, BE349958, AI221384, W44965, R64181, AI262728, AI935879, AI200164, AA770211, H00220, AI200212, AI015055, AI148686, AI122816, AW292442, AA806026, AW182515, AW468941, AA946623, AA281083, AI024474, AW104815, AA908206, BF037752, AI569420, R82204, AA588152, AI278716, AI568295, AI125585, T33608, AI383159, R73475, BG231876, AA524768, AW087900, AA953876, AA811083, R77814, AW264307, R79384, BG011965, AA456606, AA565569, W74086, AA022667, AI356156, BG033627, H41673, AA864339, AA703088, R64093, AW081075, AI264517, BE672848, AA399384, AA831635, AA455244, AA437314, H40235, R86852, R82765, AA308193, T33861, AI138975, R68595, H00614, AI025694, W67142, R33018, W80786, AI472895, R80918, AI183287, R69007, W44805, AA350061, F36345, BF718520, BF197930, BE675867, R80917, H85560, AI692850, AI203702, AA807227, W67385, AA831118, H03453, R68390, AA465624, BF961260, BE819178, R69008, R89632, AI826281, R81222, T07999, H43702, R78182, R87944, AA831315, R46331, AA045502, AI351258, H00173, AA007650, AI372636, BE675626, AA514478, AI685955, R31036, AI686215, H40234, R27714,

					W80893, AI215166, AA722459, BE261763, BE259600, AA040607, AA766842, T33436, AW148921, T33664, AI696556, BE856135, AA683541, AI220680, H03537, H66462, R37563, BE259417, H94445, R36720, W68021, AA767709, AA627884, BF823469, AA603453, AI984877, R73474, R46418, BG056248, R27713, AA437045, H26978, T03626, AI914606, AA022766, AI076842, AA865073, T33964, AI371308, R82259, AW079562, R31520, F21470, BF951552, AA807858, R31525, AI372635, R31030, N93814, and AF257319.
HLYBI15	61	645262	1 - 1065	15 - 1079	AW972599, AW972743, AW975048, AW970887, AW970588, AW971379, AW970992, AW979200, AW975259, AW971949, AW974094, AW971374, AW979241, AW970981, AW971073, AW979102, AW974354, AW972754, AW972751, AW971960, AW972828, AW971167, AW971037, AW971983, AW968339, AW975675, AW975135, AW968194, AW970980, AW972752, AW975634, AW972358, AW972744, AW970929, AW970964, AW972858, AW971113, AW975086, AW975012, AW975655, AW970967, AW979156, AW971192, AW976034, AW973808, AW975113, AW975409, AW969672, AW972367, AW975573, AW975902, AW970909, AW979096, AW970064, AW976008, AW969856, AW971987, AW972802, AW975664, AW979245, AW975094, AW970914, AW970036, AW971163, AW968167, AW979272,

				AW979050, AW970922, AW973952, AW974283, AW975694, AW969946, AW971071, AW979193, AW979229, AW970564, AW979000, AW973218, AW973176, AW968340, AW974076, AW971360, AW974824, AW974997, AW979292, AW969941, AW972621, AW971131, AW979240, AW972846, AW973828, AW972741, AW975985, AW974344, AW973376, AW971263, AW975072, AW974110, AW975146, AW972282, AW971249, AW975894, AW972271, AW973116, AW971237, AW970058, AW971020, AW976030, AW971203, AW968191, AW970078, AW971124, AW975578, AW971215, AW975571, AW968178, AW975006, AW979100, AW972302, AW972417, AW974371, AW973160, AW970932, AW975176, AW973996, AW969751, AW973183, AW970574, AW970971, AW973771, AW975213, AW973757, AW973995, AW970962, AW971115, AW971051, AW972659, AA443390, AW973204, AW971214, AW969753, AW971097, AW971981, AW968150, AW979148, AW975117, AW974117, AW969966, AW975987, AW974813, AW979184, AW972727, AW979101, AW971333, AW975663, AW971189, AL134524, AW973998, AW971985, AW972790, AW971033, AW974389, AW971045, AW972897, AW971942, AW970911, AW974890, AW971257, AW970921, AW971135, AW970024,

				AW974933, AW979129, AW975035, AW972699, AW975222, AW772696, AW979139, AW975348, AW973720, AW975425, AW971204, AW970606, AW973746, AW974370, AW979220, AW972864, AW979219, AW971416, AW970958, AW969784, H15295, AW975645, AW970896, AL031289, AC011462, AC005622, AC006146, AC011495, AC004686, AC006449, AC004383, AC005914, AL136504, AC009362, AL035495, AL138807, AC010527, AL139286, AC002316, AC027319, AC008892, AL139100, AC005566, AC006530, AC004805, AC006241, AL023553, AC005250, AL353602, AP000355, AL033529, AC005899, AP001753, AC074331, AC004867, AC003047, AC020626, AL080243, AC000085, Z83840, AC005632, Z98036, AC010412, AL008718, M26434, AC008569, AC004139, AC004477, AC003957, AL022318, AC004858, AP001685, AC011451, AL035072, AC004895, AL021155, AF109907, AC008753, AL133230, AL035458, AL050318, AC004583, AC005694, AC005098, AL121658, AC005031, AC006080, AC004832, AL117258, AC005049, AC005081, AC005522, AC004971, AC004167, AC007917, AF053356, AL163249, AC008623, AC005781, AC004166, AL022323, AC005544, AL356354, AL118520, U91318, AC004777, AC004996, AC004408, AC005225, U80017, AL355476, AL021393, AL022320, AC005015, Z98200, Z81314,

						AC004019, AP000140, AC008760, Z83838, AC005527, AL109825, AL121928, AL354750, AC007666, AC012309, AC004534, AL162430, Z93015, AC010519, AL035659, AL158832, AL132653, AP001727, AP001711, Z82188, AC016637, AC004491, AC004980, AC004033, AL354914, and AL354914.
HMEJE05	62	722231	1 - 1914	15 - 1928		BE292961, BE300470, BE298159, AV701105, BF791212, AV717352, AV693678, AV717186, AW962353, AI814288, AV763685, AL522728, AW966815, AA442919, BF962776, AW401801, AW962349, AI376871, AA305112, AI380212, AI683132, AI860202, BE743268, AA099733, AA099732, BF956120, AW627633, AI754022, AV764521, AI630537, BE206347, BF837353, AW966817, AI439469, AW630915, AA724473, AW183349, AV742743, BE019157, BF835349, BF960834, BF962781, BE874961, AA249097, BF961479, AI378222, BF110710, BE762832, AK027012, and AF168711.
HNGIX55	63	695749	1 - 767	15 - 781		AU140348, AU138078, AU136503, AV731936, AW814395, AL043065, AI868368, AI922061, AA569180, AA613221, AA501775, AA584099, AA664366, T62761, AA489896, D59168, BF985200, H54464, AA504977, BE304382, AA720764, AL044254, N86026, BF945554, T02940, AA376315, AC006249, AC007690, AC002449, AL121782, AC005034, AL136307, U69730, AC000125, AC005029, AL035695, AL353999, AK002154, AL136520, AL138478, AL121575, AK023773, AL136133, AK002104,

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HNHEX30	64	634848	1 - 1180	15 - 1194		BF869510, BF870168, BF868734, BF379935, AI245870, AW843982, AA628010, BF743745, AA076920, BF081565, AW854413, AW854493, AW854488, AC005488, AC018720, AC004980, AB014518, AC005236, AC005236, AC004980, AC004980, AC005488, AC005488, AC018720, AC018720, and AC018720.
HPJBI33	65	685699	1 - 1663	15 - 1677		AI679782, BE796439, AV763892, BE387734, AW303196, AW301350, AW274349, AL046409, AI204304, AU148742, AL048142, F36273, BF475381, BE156019, AL041690, BE872393, N94311, BG236735, AA599480, AW630298, AW473163, AI754955, BF683672, AI281881, AW276827, AI341548, BF806176, AW467362, BF805094, BF940837, AV762050, BE350475, AA631507, AV652936, AW963497, BF965007, AV681599, BE042649, AV762139, AW080939, AW276435, AI291268, AI291124, AW339568, AU154961, AA426277, AI133164, AW088616, AI951863, AW873530, BF816072, AL038785, AW148792, AW338086, BE869857, AW408717, BE042475, AI580652, AA525190, AL044940, AV760466, AV713243, AW969694, AI537955, AC005527, AL050318, AC000025, AF134726,

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HRABA80	66	588460	1 - 1223	15 - 1237		AU147250, F24079, AI791459, AI732503, AA523577, AI791342, AU121439, BF309840, BF308519, AI659402, AA719317, AA602233, AI752815, AW967109, AV694013, AA470486, AI218622, AA644545, AK022184, AC005777, AL031431, AC007406, AC004143, AC006131, AC005760, AC005529, AL354766, AC005544, AL035079, AL356299, AL031297, AC005778, AC011666, AL035071, AL136529, and AL356740.
HRACD80	67	882163	1 - 1920	15 - 1934		BF001770, AI431600, AI332903, AW778829, BF197765, AI814110, BF509841, BF875981, AI983390, AI741104, AI263763, AA719400, AL354898, and AL354898.
HSLCX03	68	889145	1 - 3286	15 - 3300		BF205433, BG025867, BF206942, AV729983, AV706183, AV732002, AV706746, AV752043, AV731759, BE867291, AV725927, AV723449, AV731977, AV702427, AV730711, AV751573, AV730171, AV731694, AV731043, AV751921, AV731744, AV731313, AV752443, AV728270, AV732653, AV706724, AV726505, AV752447, AV758481, AV730781, AV753374, AV732149, AV730288, AV711496, AV730816, AV730165, AV710938, AV731708, AV710534, AV732353, AV730547, AV731275, AV659189, AW247024, AI814360, AV757088, AW665404, AV702798, AV701611, AV726674, AV707783, AV702409,

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HT5GJ57	69	740767	1 - 1783	15 - 1797	AW574516, BG259057, BF975647, AW575080, BF795582, BE559713, BE396519, AI521311, BE397179, AW237047, AI446257, BF238156, BF663664, AI862389, AI573063, BE513368, AW296989, AU157608, BF128855, AA811488, AA827120, AW338778, AI439638, BE560794, AI250231, BG120258, AI312540, AA633095, AV742373, AI343438, AA604586, BE269253, AI669176, AI149413, AA723128, AW403042, AA722908, W57991, AI826124, BE246032, AU138425, BE513265, AI865336, AI219708, AI589599, AW732709, H23560, AA765412, AI589912, BE560732, T61448, AW444827, AA594614, AA648496, AA361096, N34423, W58075, AV742389, N48728, AA975334, AA731435, AA166766, BE247378, AA810638, AW298682, AI919140, AW402333, AI341517, BE245894, AV743440, AI962720, BF062274, T30849, AI982795, AW405561, T25945, AA810222, AA807717, Z39117, AV756294, AV724221, BG120887, AA593214, N48658, AW083122, AA639378, H23535, AI492348, AI656821, AF045555, AK002099, AF257135, AF161531, AC005081, AF086239, AC016675, AC016675, AC005081, and AC005081.
HTACS42	70	722253	1 - 1359	15 - 1373	AL538414, BF526452, BF526536, BF526493, BF973770, BE312752, BF311801, BG110390, BF338594, BE781152, BE879539, BG168442, BE264360, BF686397, BE545473, BF684020, BF340262, AL537916, BF245363, BE737756, BF697202, AW130967, AI310162, BE301024, BF700864, AA054583, BF381567, AI422243, AI800437, AL537915, AA461187,

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HTEKE40	71	740768	1 - 1565	15 - 1579		BF940114, AI361316, BG223420, AA876320, AL356216, AL356216, AC027430, and AC027430.
HTOBX69	72	722255	1 - 1014	15 - 1028		AW273804, AA488861, AW968924, AA488938, AI093600, BE173122, AW206450, AA635743, BF222008, AI288448, AI344556, AI800674, AA284257, AA505427, AA588588, N30779, AI149444, AL523271, AA886990, AI015520, AI248194, BE965684, AA458483, BE544421, AA004285, AK000672, AX026129, AF151848, AC004997, and AC005585.
HUVEO77	73	740776	1 - 3660	15 - 3674		AL523087, AL523086, AV727906, BF511581, AV707732, BE883906, AV727224, AW964463, AW003008, AV702158, AV705108, BE887170, AA928698, AA436935, AL041085, BE048631, BF515047, BE884186, BF672714, AI888610, BE549984, BF105274, AI627792, BE138759, BE876805, AW954912, AW959529, BF693086, AI446742, AI332607, W60846, BE674526, BF790798, AA824382, BF694509, BF901184, AI610338, BF433383, W37870, W56436, BE677261, AA486366, AI936599, AI925670, AW451948, AV728172, AA548758,

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H2CBG48	74	745365	1 - 2783	15 - 2797	AL536879, AL536880, AW974652, BF978951, AI761251, AI655763, AA307225, AA628063, AW043567, AW376300, AI693827, BE047125, AI129587, AI701013, AA651730, AW172361, AW339506, AW085916, AA457150, AA052951, AI582629, AV688972, BF820514, AI590194, AW085909, AA916242, AI000008, AA962570, N52070, AA293021, AI371342, BF891108, AA058439, BF946218, BF891008, AV689991, AV690900, AI458885, AI962506, H40784, AI364207, AA464514, AW994164, BF946219, AV656660, BF891112, AA336322, AA337109, AI824603, AA336509, AA336407, BF036975, AA337222, N46906, AA464515, AA319240, AA765507, AW361203, AA053434, AI928199, AW299270, AV713792, N50282, AA056762, BE708029, AW361192, W07762, AL513817, BE965014,

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H2CBU83	75	884134	1 - 2689	15 - 2703	BE613316, BE739453, AW961199, AV658769, BE785673, AW963999, BF037119, BG030580, BF036149, BF699154, BF033837, BF697524, BF695458, BF036638, BF701778, BG030507, AW377122, BF665913, BF699078, AW377125, BF665294, AV658829, BF667082, BG166746, AW851261, BF241480, AW850925, AI978869, BF695890, AA845339, BF668201, BF699860, BF085620, AA405940, BE612726, BF666583, BF667787, BE739116, BF665805, AW752845, BF701466, AI800939, BG121547, AI620357, BF700054, AW851052, AI924880, AW752835, AI800807, BF697582, BF700919, BF667321, AI139396, BE958619, AV692286, AI955392, AW752844, BE042841, BF698625, BF244588, AW440250, BF698345, AW152584, AW955901, AI671911, AA535832, AW850982, AI935579, BE089877, AW752868, AI683119, BF130660, D61864, AW630835, AI621153, BF514638, BF697211, AW192136, AI286255, AA403153, D62117, AW028833, N78154, BF154792, BF665821, AI538061, N64201, AW851056, AW938593, BE093579, AW938596, AA928873, AV651183, BE817020, AV657915, AV657131, BF666276, AV660141, AI699025, AI016115, R66206, N45586, D61708, BE868472, AA403241, AV657914, AA313513, AV682813, H88565,

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HAPNY94	76	699770	1 - 728	15 - 742		BG029349, AW384082, AI653230, AW384103, AW590965, AI952047, AW474522, BF514114, AI952951, AI138532, AI199860, AW474480, AI655852, AI656352, AV727834, AI424794, AA909918, AI377297, AA632416, AA205078, BG150070, BE243783, AA709293, AW016441, AA906134, AI350684, AI825691, AW770135, AA971473, U51144, BE867482, AA770535, AA873641, BE160147, BF772564, BE184408, AC013339, AC013339, AL133351, and AL133351.
HBJHZ58	77	745372	1 - 1811	15 - 1825		AA370047, AA370019, AL041562, AA581433, BF851009, AL041521, AA843874, AA985136, AA111953, BF935428, AI126075, W25952, AU146079, AI299358, BE671252, BE867935, BE379085, AA176997, AA773359, AW166737, AU150602, AA219042, R89180, AI909852, L11910, AL390035, AL450169, AC009228,

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HCE2B33	78	745399	1 - 1660	15 - 1674		BE250543, BE250657, AL520610, AW955817, BE409837, BE886243, BF033602, AI826453, BE393689, BE378093, AI804861, BE743664, AW250030, AI971716, BE552024, AI140361, AI659632, AW452114, AI479198, AW779955, AW197198, AW590289, BF002997, N79585, AI144134, AI799889, BG032437, AI203257, AI358934, N64394, W16574, AL520611, H12263, BF509683, BE856425, AI351628, R14214,

					H12264, AI817266, AA332565, R40631, AI650967, R54427, R40632, AW450259, AI523692, BG104378, F10829, R87336, R14215, BE385368, BE890335, AF150132, BF345824, AV739421, AW955816, AW081695, AA235053, BF125714, and AK025813.
HDPBQ02	79	745403	1 - 2177	15 - 2191	BF346320, AW972888, BE796439, AL048969, AV722075, BF673911, AU118837, AV720115, BF828714, AV763305, BE155132, AA525174, AV728369, BF826830, AI694178, AI653525, AV761562, AL044340, AU145476, BE908602, AW089861, BF901147, AU147226, BG110480, BG028665, BG034591, AL037632, AA527963, AI457389, AW970987, AV699393, AL044339, AW965008, AA577824, AU148007, AU146981, AV700663, AW504011, BE973855, AI831816, AW850396, AU120100, AA572983, BF529925, AL042310, AL119331, AI925665, AV700545, AW970588, BF347042, AA525807, AA631638, AV759046, AI251024, BE541237, BF892846, AW188427, AF074667, AA224525, AA551204, BG026818, AA601230, AV719084, AU151751, AV722030, AL042906, AA129272, AA807556, BF345114, AA557457, AV754399, AI983645, AU155359, BF968610, T57096, AV762002, BF694054, AV760497, AW502873, BF882222, AW510513, AA019966, AL532829, AA836811, AU155104, BG032943, AL042905, AA904211, AI251696, AI254508, AW962006,

				AA713829, AU157011, AV700498, AL048901, AV725627, AA297145, AV762838, AA507526, AA838140, AA578832, AA856817, BF345228, AA626632, AL044489, BE538259, BF240672, BG026977, AW089625, BE675240, BF882223, AW440545, BF346854, AC010412, AC005081, AC008753, AC009516, AF111168, AC018751, AF109907, AL034405, AP001760, AP000501, AL109614, AC004813, AC002470, AC013429, AC002563, AC004166, Z98200, AF134726, AP000688, AL132713, AC011500, AL158198, AC007216, AC004832, AL136137, AC009032, AL358372, AC006285, AC005180, AL049776, AL137230, U91326, AC002544, AC004686, AC004383, AL133163, AC004655, AL049709, AL035249, AC009060, AL109743, AC004089, AC005484, AL136179, AC005920, AC004216, AP001724, AC008543, AC006345, AC005049, AF001549, AC006441, AL157838, AC016395, AC005052, AC006141, U85195, Z84487, AC007546, AC005412, AC005323, AC007371, AL138783, AP001728, AL022316, AC008569, AP001714, AC008752, AP001711, AC004638, AC005913, AC005736, AP001713, AC006511, AP001053, AE000658, AL135924, AC005694, AC002477, AC008738, AL031680, AL161670, AC006480, AL035659, AC005015, AP000065, AC025588, AC005488, AL163249, AC015853, Z99716, AL034429, AC011477, AF088219, AL109963, AC011464, AC009228,

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HFIYI70	80	744906	1 - 1321	15 - 1335	BF345869, AV726707, BE301105, BG034889, AW360850, W19606, BF446277, AU148126, BE250349, AU149480, AU152860, AU148657, AU148883, AW418817, AW862152, AW003619, BE672523, BF350928, BE909817, BE208094, BE159456, AI697801, BF108425, AI969149, AW301720, BE073395, AA132979, BF111388, BF690067, AW612712, BF540929, N23638, AA889907, T87882, BF373283, H25796, AW606625, R51344, AW082596, AI910259, AA349693, AA860167, AI668892, T87971, BF593061, R48370, BF807501, AI364176, R39999, BE740663, AA640793, BF210703, N71593, AW016249, R48270, BE258960, R59020, BE819678, AA360038, AI700434, BE077265, AI076309, AI783692, BE742022, BF476374, AI798645, BE747651, BE730294, H05971, R51451, AI825888, N94965, BF773032, BE839417, U90730, U90731, AK024760, AK022451, AK024036, AK022740, AB045989, T63351, T63674, R49212, R59159, R64065, R66441, R76632, R80386, R80492, H03457, H03542, H20303, H20987, R89247, R89248, R98830, R99313, H48284,

					H50118, H56131, H64163, H78393, H93783, H93875, N26313, N29711, N32029, N33057, N34497, N39756, N42121, N42238, N47780, N57738, N58187, N58647, N64442, N67758, N70951, W48757, AA024815, AA024921, AA031973, AA053392, AA085909, AA129251, AA132937, AA133081, AA146728, AA147067, AA147069, AA258537, AA424525, AA428935, AA429150, AA429385, AL353755, AL353755, AC023020, and AC023020.
HDPOZ56	81	815653	1 - 1853	15 - 1867	AI859620, AI830021, AI949469, AI887204, AI218392, AW511272, AW194364, AA970014, AI307671, AW582666, AI873619, AW609988, AA693331, AI868204, AW079432, AI540674, AI537643, AV753074, AI800179, AI245748, AW193467, AA580663, AI537677, AI499913, AI560545, BG029829, AI564448, AI345688, AW162194, AW083572, BF680133, AA575874, AI540606, AI584130, AI564234, AI690887, BG107995, AW834282, AI358209, AA056265, AW050578, AI473451, AA485953, AW129589, AA641818, AA939199, BF871314, AI819663, AI525669, AI623941, AW827206, AW051088, AI758309, AI225000, AI961278, AW195253, AI621341, AI561356, AI690748, AW075382, AI783821, AI470648, AI927233, AI589428, AI860027, BE397784, BF572734, F28295, AW021373, AI859991, AI700159, AI635038, N27632, AW161202, BF836332, AI352326, AI619723, AI612885, AI814087, AW163834, AI636619, AI932739, AV682575, BF753053, BF997967, BF699668, AI956086, AW022636, BE907440,

				N98597, AW191844, AI524654, AI473536, AW075484, BG113299, AW089233, AI590043, AI620866, AI628325, AI678446, AI538885, AW073721, AL040241, AW081606, W60514, AW168768, AI802372, AI922812, AW168296, AI587156, AI581033, AI932458, BF339548, AI336634, AL037463, AI741158, AW022682, AI887389, AW081383, AI247193, AA070889, AW151136, AI349622, AI270295, AW193344, AI471282, AI933992, AI499131, AA847199, AL045413, AI627714, AW117675, AI888621, AI890907, AI926669, AI630876, AA835966, BF921291, AI784219, AV758339, AI281757, AI627988, AI432644, BG167393, AI582932, AW090393, AI872423, AV747571, AI500061, BG254284, AI434731, BF103211, BG001293, AI659043, AI758270, AI479292, AA502794, AI620037, AI569367, AI469801, AI573167, BE874133, AW082532, AW238753, AI570056, AI686749, BF895218, AW020592, AI440238, BF814072, F37419, AL048871, N75779, AW102902, AI478123, AW087199, AW161098, AW022494, AV750565, AW020288, BF811808, BE963159, AI702527, AI446823, AI688848, BG114724, AW089572, AI494201, BF872670, AW263804, AI289791, AI804505, AI885512, AW080076, AI582912, N29277, AI631216, BE540578, AI366959, AI697157, AA761557, AL048323, AI287476, AI431323, AI961414, AI335476, BF032768, AW073907, AW438793, AL048340, AI282346, N25033, AI826225, AW008226, BE393784, AI349937, AI805598, BG261310, AI334884, AI307543,

				AI918408, AI491710, AI345114, AI434134, AI911648, BE138712, AI345251, BF811804, AW071412, AI349957, AI254226, AW088560, AI568061, BF341908, BG169738, AI307210, AI307708, AI336513, BE885353, AI312325, AW071395, AI336662, AV738918, AI500659, AV717389, AI702301, AI564765, BG167986, AI784233, U70429, U70430, AC011452, AL389935, AK027116, I48978, AL137665, AF111112, AJ250403, AK025099, AF210052, AL050149, AR083266, AL157480, AK026541, AK027146, I89947, A18777, AF087943, AR038854, A07647, AL110218, AF111849, U86379, AF116646, AK025015, AL137558, L13297, AL355701, AF116691, AL049339, E07108, AF260566, AB048994, AX006386, AF260436, I00734, AK024524, AK026389, AK000603, A77033, A77035, X83544, AK000137, AF109155, AF132730, AF026124, AF205861, E00617, E00717, E00778, AF177401, AL442082, AL133054, A08913, AK000655, I48979, AF130066, AK026534, AF115392, I89931, AF159141, A08912, S77771, A08910, A08911, AR087170, A08909, AL049464, A52563, AL357195, AR073709, X76228, A08907, A21103, A08908, AJ299431, AB044547, AL137574, S79832, S76508, AL110222, AF022363, I89934, AJ005690, AF314091, AL136884, AL359622, E05822, AK026057, AF130054, AF119860, AF130075, A18788, AC004200, AF022813, Y10655, A07588, AK025391, AL162004, AK026744, AK025119, AF227198, AL049347, AF113691, AC006451, AK026647, S78453, AF162782,

				AB047941, AK025084, AB050421, AL157479, S82852, AL137488, AF230496, AK026542, AF130055, AF215669, AL080159, I33392, D44497, AL355719, I52013, AK025350, AF155221, AF017790, AB038698, AB040710, E01314, A58545, Y14314, AX015425, AJ003118, AF061981, AF321617, AL050155, AL096751, U79523, AL137550, AF055917, AK024538, AF130059, U75932, S75997, AK024588, AK024992, S36676, AK024533, AK026480, AL137478, I80064, AL359596, AF116609, Z82022, AF116650, AF075763, AK026762, AF183393, AF113222, AK027164, X59812, AL122098, AF106697, AF151109, AL137529, AF026008, AK027142, I09499, AF130082, A45787, AF217991, AL096720, AL080126, AL050138, U35846, AL137480, AL110280, AL359618, D55641, AL133067, A57389, AF116676, AF131773, AF218031, AL050277, E04233, AB048919, AF111851, AK000257, AF090903, AL096744, AB047609, X65873, AJ006417, AF061573, D83032, AL137537, E02914, AF036941, AK027095, AB050410, AK025906, AX005848, AL049314, AX005804, AF143957, M85165, AK026844, AF126488, U00686, AF040751, AF199027, X72387, I89944, A15345, AL137463, AF119899, Y11587, AL137530, AK024601, AF225424, AL122106, E12579, Z13966, AK024974, AK027144, AF061795, AF151685, AL133016, AK025113, L31396, AK024545, U57352, AF267849, AB032264, AF004162, AL359620, AR068466, L31397, AL389939, AF115410, AK026462, E12747, AL080124, and


AF067790.

Table 4

Code	Description	Tissue	Organ	Cell Line	Disease	Vector
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				

AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs					
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs					
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.					
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs					
AR054	Donor II Resting B Cells	Donor II Resting B Cells					
AR055	Heart	Heart					
AR056	Human Lung (clonetech)	Human Lung (clonetech)					
AR057	Human Mammary (clontech)	Human Mammary (clontech)					
AR058	Human Thymus (clonetech)	Human Thymus (clonetech)					
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)					
AR060	Kidney	Kidney					
AR061	Liver	Liver					
AR062	Liver (Clontech)	Liver (Clontech)					
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia					
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma					
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma					
AR066	normal breast	normal breast					
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)					
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045					
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208					

AR070	Normal Ovary 9806G005	Normal Ovary 9806G005					
AR071	Ovarian Cancer	Ovarian Cancer					
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)					
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)					
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)					
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)					
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)					
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)					
AR078	ovarian cancer 15799	ovarian cancer 15799					
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID					
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1					
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1					
AR082	ovarian cancer 94127303	ovarian cancer 94127303					
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304					
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029					
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045					
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001					
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC					
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd					

AR089	Prostate	Prostate					
AR090	Prostate (clonetech)	Prostate (clonetech)					
AR091	prostate cancer	prostate cancer					
AR092	prostate cancer #15176	prostate cancer #15176					
AR093	prostate cancer #15509	prostate cancer #15509					
AR094	prostate cancer #15673	prostate cancer #15673					
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)					
AR096	Spleen	Spleen					
AR097	Thymus T cells activated	Thymus T cells activated					
AR098	Thymus T cells resting	Thymus T cells resting					
AR099	Tonsil	Tonsil					
AR100	Tonsil geminal center centroblast	Tonsil geminal center centroblast					
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell					
AR102	Tonsil lymph node	Tonsil lymph node					
AR103	Tonsil memory B cell	Tonsil memory B cell					
AR104	Whole Brain	Whole Brain					
AR105	Xenograft ES-2	Xenograft ES-2					
AR106	Xenograft SW626	Xenograft SW626					
AR119	001: IL-2	001: IL-2					
AR120	001: IL-2.1	001: IL-2.1					
AR121	001: IL-2_b	001: IL-2_b					
AR124	002 : Monocytes untreated (1hr)	002 : Monocytes untreated (1hr)					
AR125	002 : Monocytes untreated (5hrs)	002 : Monocytes untreated (5hrs)					
AR126	002: Control.1C	002: Control.1C					
AR127	002: IL2.1C	002: IL2.1C					
AR130	003 : Placebo-treated Rat	003 : Placebo-					

	Lacrimal Gland	treated Rat Lacrimal Gland				
AR131	003 : Placebo-treated Rat Submandibular Gland	003 : Placebo-treated Rat Submandibular Gland				
AR135	004 : Monocytes untreated (5hrs)	004 : Monocytes untreated (5hrs)				
AR136	004 : Monocytes untreated 1hr	004 : Monocytes untreated 1hr				
AR139	005: Placebo (48hrs)	005: Placebo (48hrs)				
AR140	006: pC4 (24hrs)	006: pC4 (24hrs)				
AR141	006: pC4 (48hrs)	006: pC4 (48hrs)				
AR152	007: PHA(1hr)	007: PHA(1hr)				
AR153	007: PHA(6HRS)	007: PHA(6HRS)				
AR154	007: PMA(6hrs)	007: PMA(6hrs)				
AR155	008: 1449_#2	008: 1449_#2				
AR161	01: A - max 24	01: A - max 24				
AR162	01: A - max 26	01: A - max 26				
AR163	01: A - max 30	01: A - max 30				
AR164	01: B - max 24	01: B - max 24				
AR165	01: B - max 26	01: B - max 26				
AR166	01: B - max 30	01: B - max 30				
AR167	1449 Sample	1449 Sample				
AR168	3T3P10 1.0uM insulin	3T3P10 1.0uM insulin				
AR169	3T3P10 10nM Insulin	3T3P10 10nM Insulin				
AR170	3T3P10 10uM insulin	3T3P10 10uM insulin				
AR171	3T3P10 No Insulin	3T3P10 No Insulin				
AR172	3T3P4	3T3P4				
AR173	Adipose (41892)	Adipose (41892)				
AR174	Adipose Diabetic (41611)	Adipose Diabetic (41611)				
AR175	Adipose Diabetic (41661)	Adipose Diabetic (41661)				

AR176	Adipose Diabetic (41689)	Adipose Diabetic (41689)					
AR177	Adipose Diabetic (41706)	Adipose Diabetic (41706)					
AR178	Adipose Diabetic (42352)	Adipose Diabetic (42352)					
AR179	Adipose Diabetic (42366)	Adipose Diabetic (42366)					
AR180	Adipose Diabetic (42452)	Adipose Diabetic (42452)					
AR181	Adipose Diabetic (42491)	Adipose Diabetic (42491)					
AR182	Adipose Normal (41843)	Adipose Normal (41843)					
AR183	Adipose Normal (41893)	Adipose Normal (41893)					
AR184	Adipose Normal (42452)	Adipose Normal (42452)					
AR185	Adrenal Gland	Adrenal Gland					
AR186	Adrenal Gland + Whole Brain	Adrenal Gland + Whole Brain					
AR187	B7(1hr)+ (inverted)	B7(1hr)+ (inverted)					
AR188	Breast (18275A2B)	Breast (18275A2B)					
AR189	Breast (4004199)	Breast (4004199)					
AR190	Breast (4004399)	Breast (4004399)					
AR191	Breast (4004943B7)	Breast (4004943B7)					
AR192	Breast (4005570B1)	Breast (4005570B1)					
AR193	Breast Cancer (4004127A30)	Breast Cancer (4004127A30)					
AR194	Breast Cancer (400443A21)	Breast Cancer (400443A21)					
AR195	Breast Cancer (4004643A2)	Breast Cancer (4004643A2)					
AR196	Breast Cancer (4004710A7)	Breast Cancer (4004710A7)					
AR197	Breast Cancer	Breast Cancer					

	(4004943A21)	(4004943A21)						
AR198	Breast Cancer (400553A2)	Breast Cancer (400553A2)						
AR199	Breast Cancer (9805C046R)	Breast Cancer (9805C046R)						
AR200	Breast Cancer (9806C012R)	Breast Cancer (9806C012R)						
AR201	Breast Cancer (ODQ 45913)	Breast Cancer (ODQ 45913)						
AR202	Breast Cancer (ODQ45913)	Breast Cancer (ODQ45913)						
AR203	Breast Cancer (ODQ4591B)	Breast Cancer (ODQ4591B)						
AR204	Colon Cancer (15663)	Colon Cancer (15663)						
AR205	Colon Cancer (4005144A4)	Colon Cancer (4005144A4)						
AR206	Colon Cancer (4005413A4)	Colon Cancer (4005413A4)						
AR207	Colon Cancer (4005570B1)	Colon Cancer (4005570B1)						
AR208	Control RNA #1	Control RNA #1						
AR209	Control RNA #2	Control RNA #2						
AR210	Cultured Preadipocyte (blue)	Cultured Preadipocyte (blue)						
AR211	Cultured Preadipocyte (Red)	Cultured Preadipocyte (Red)						
AR212	Donor II B-Cells 24hrs	Donor II B-Cells 24hrs						
AR213	Donor II Resting B-Cells	Donor II Resting B-Cells						
AR214	H114EP12 10nM Insulin	H114EP12 10nM Insulin						
AR215	H114EP12 (10nM insulin)	H114EP12 (10nM insulin)						
AR216	H114EP12 (2.6ug/ul)	H114EP12 (2.6ug/ul)						

AR217	H114EP12 (3.6ug/ul)	H114EP12 (3.6ug/ul)					
AR218	HUVEC #1	HUVEC #1					
AR219	HUVEC #2	HUVEC #2					
AR221	L6 undiff.	L6 undiff.					
AR222	L6 Undifferentiated	L6 Undifferentiated					
AR223	L6P8 + 10nM Insulin	L6P8 + 10nM Insulin					
AR224	L6P8 + HS	L6P8 + HS					
AR225	L6P8 10nM Insulin	L6P8 10nM Insulin					
AR226	Liver (00-06-A007B)	Liver (00-06-A007B)					
AR227	Liver (96-02-A075)	Liver (96-02-A075)					
AR228	Liver (96-03-A144)	Liver (96-03-A144)					
AR229	Liver (96-04-A138)	Liver (96-04-A138)					
AR230	Liver (97-10-A074B)	Liver (97-10-A074B)					
AR231	Liver (98-09-A242A)	Liver (98-09-A242A)					
AR232	Liver Diabetic (1042)	Liver Diabetic (1042)					
AR233	Liver Diabetic (41616)	Liver Diabetic (41616)					
AR234	Liver Diabetic (41955)	Liver Diabetic (41955)					
AR235	Liver Diabetic (42352R)	Liver Diabetic (42352R)					
AR236	Liver Diabetic (42366)	Liver Diabetic (42366)					
AR237	Liver Diabetic (42483)	Liver Diabetic (42483)					
AR238	Liver Diabetic (42491)	Liver Diabetic (42491)					
AR239	Liver Diabetic (99-09-A281A)	Liver Diabetic (99-09-A281A)					
AR240	Lung	Lung					
AR241	Lung (27270)	Lung (27270)					

AR242	Lung (2727Q)	Lung (2727Q)					
AR243	Lung Cancer (4005116A1)	Lung Cancer (4005116A1)					
AR244	Lung Cancer (4005121A5)	Lung Cancer (4005121A5)					
AR245	Lung Cancer (4005121A5))	Lung Cancer (4005121A5))					
AR246	Lung Cancer (4005340A4)	Lung Cancer (4005340A4)					
AR247	Mammary Gland	Mammary Gland					
AR248	Monocyte (CT)	Monocyte (CT)					
AR249	Monocyte (OCT)	Monocyte (OCT)					
AR250	Monocytes (CT)	Monocytes (CT)					
AR251	Monocytes (INFG 18 hr)	Monocytes (INFG 18 hr)					
AR252	Monocytes (INFG 18hr)	Monocytes (INFG 18hr)					
AR253	Monocytes (INFG 8-11)	Monocytes (INFG 8-11)					
AR254	Monocytes (O CT)	Monocytes (O CT)					
AR255	Muscle (91-01-A105)	Muscle (91-01-A105)					
AR256	Muscle (92-04-A059)	Muscle (92-04-A059)					
AR257	Muscle (97-11-A056d)	Muscle (97-11-A056d)					
AR258	Muscle (99-06-A210A)	Muscle (99-06-A210A)					
AR259	Muscle (99-07-A203B)	Muscle (99-07-A203B)					
AR260	Muscle (99-7-A203B)	Muscle (99-7-A203B)					
AR261	Muscle Diabetic (42352R)	Muscle Diabetic (42352R)					
AR262	Muscle Diabetic (42366)	Muscle Diabetic (42366)					
AR263	NK-19 Control	NK-19 Control					

AR264	NK-19 IL Treated 72hrs	NK-19 IL Treated 72hrs					
AR265	NK-19 UK Treated 72 hrs.	NK-19 UK Treated 72 hrs.					
AR266	Omentum Normal (94-08-B009)	Omentum Normal (94-08-B009)					
AR267	Omentum Normal (97-01-A039A)	Omentum Normal (97-01-A039A)					
AR268	Omentum Normal (97-04-A114C)	Omentum Normal (97-04-A114C)					
AR269	Omentum Normal (97-06-A117C)	Omentum Normal (97-06-A117C)					
AR270	Omentum Normal (97-09-B004C)	Omentum Normal (97-09-B004C)					
AR271	Ovarian Cancer (17717AID)	Ovarian Cancer (17717AID)					
AR272	Ovarian Cancer (9905C023RC)	Ovarian Cancer (9905C023RC)					
AR273	Ovarian Cancer (9905C032RC)	Ovarian Cancer (9905C032RC)					
AR274	Ovary (9508G045)	Ovary (9508G045)					
AR275	Ovary (9701G208)	Ovary (9701G208)					
AR276	Ovary 9806G005	Ovary 9806G005					
AR277	Pancreas	Pancreas					
AR278	Placebo	Placebo					
AR279	rIL2 Control	rIL2 Control					
AR280	RSS288L	RSS288L					
AR281	RSS288LC	RSS288LC					
AR282	Salivary Gland	Salivary Gland					
AR283	Skeletal Muscle	Skeletal Muscle					
AR284	Skeletal Muscle (91-01-A105)	Skeletal Muscle (91-01-A105)					
AR285	Skeletal Muscle (42180)	Skeletal Muscle (42180)					
AR286	Skeletal Muscle (42386)	Skeletal Muscle (42386)					
AR287	Skeletal Muscle (42461)	Skeletal Muscle					

AR288	Skeletal Muscle (91-01-A105)	Skeletal Muscle (91-01-A105)						
AR289	Skeletal Muscle (92-04-A059)	Skeletal Muscle (92-04-A059)						
AR290	Skeletal Muscle (96-08-A171)	Skeletal Muscle (96-08-A171)						
AR291	Skeletal Muscle (97-07-A190A)	Skeletal Muscle (97-07-A190A)						
AR292	Skeletal Muscle Diabetic (42352)	Skeletal Muscle Diabetic (42352)						
AR293	Skeletal Muscle Diabetic (42366)	Skeletal Muscle Diabetic (42366)						
AR294	Skeletal Muscle Diabetic (42395)	Skeletal Muscle Diabetic (42395)						
AR295	Skeletal Muscle Diabetic (42483)	Skeletal Muscle Diabetic (42483)						
AR296	Skeletal Muscle Diabetic (42491)	Skeletal Muscle Diabetic (42491)						
AR297	Skeletal Muscle Diabetic 42352	Skeletal Muscle Diabetic 42352						
AR298	Skeletal Musle (42461)	Skeletal Musle (42461)						
AR299	Small Intestine	Small Intestine						
AR300	Stomach	Stomach						
AR301	T-Cell + HDPBQ71.fc 1449 16hrs	T-Cell + HDPBQ71.fc 1449 16hrs						
AR302	T-Cell + HDPBQ71.fc 1449 6hrs	T-Cell + HDPBQ71.fc 1449 6hrs						
AR303	T-Cell + IL2 16hrs	T-Cell + IL2 16hrs						
AR304	T-Cell + IL2 6hrs	T-Cell + IL2 6hrs						
AR306	T-Cell Untreated 16hrs	T-Cell Untreated 16hrs						
AR307	T-Cell Untreated 6hrs	T-Cell Untreated 6hrs						

AR308	T-Cells 24 hours	T-Cells 24 hours					
AR309	T-Cells 24 hrs	T-Cells 24 hrs					
AR310	T-Cells 24 hrs.	T-Cells 24 hrs.					
AR311	T-Cells 24hrs	T-Cells 24hrs					
AR312	T-Cells 4 days	T-Cells 4 days					
AR313	Thymus	Thymus					
AR314	TRE	TRE					
AR315	TREC	TREC					
AR316	Virtual Mixture	Virtual Mixture					
H0004	Human Adult Spleen	Human Adult Spleen	Spleen			Uni-ZAP XR	
H0008	Whole 6 Week Old Embryo					Uni-ZAP XR	
H0009	Human Fetal Brain					Uni-ZAP XR	
H0012	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR	
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR	
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR	
H0015	Human Gall Bladder, fraction II	Human Gall Bladder	Gall Bladder			Uni-ZAP XR	
H0024	Human Fetal Lung III	Human Fetal Lung	Lung			Uni-ZAP XR	
H0028	Human Old Ovary	Human Old Ovary	Ovary			pBluescript	
H0030	Human Placenta					Uni-ZAP XR	
H0031	Human Placenta	Human Placenta	Placenta			Uni-ZAP XR	
H0032	Human Prostate	Human Prostate	Prostate			Uni-ZAP XR	
H0033	Human Pituitary	Human Pituitary				Uni-ZAP XR	
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR	
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR	
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR	
H0040	Human Testes Tumor	Human Testes Tumor	Testis		disease	Uni-ZAP XR	
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR	
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR	

H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus		disease	Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0051	Human Hippocampus	Human Hippocampus	Brain			Uni-ZAP XR
H0052	Human Cerebellum	Human Cerebellum	Brain			Uni-ZAP XR
H0053	Human Adult Kidney	Human Adult Kidney	Kidney			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus		disease	Lambda ZAP II
H0060	Human Macrophage	Human Macrophage	Blood	Cell Line		pBluescript
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0065	Human Esophagus, Normal	Human Esophagus, normal	Esophagus			Uni-ZAP XR
H0068	Human Skin Tumor	Human Skin Tumor	Skin		disease	Uni-ZAP XR
H0069	Human Activated T-Cells	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0071	Human Infant Adrenal Gland	Human Infant Adrenal Gland	Adrenal gland			Uni-ZAP XR
H0081	Human Fetal Epithelium (Skin)	Human Fetal Skin	Skin			Uni-ZAP XR
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0085	Human Colon	Human Colon				Lambda ZAP II
H0086	Human epithelioid sarcoma	Epithelioid Sarcoma, muscle	Sk Muscle		disease	Uni-ZAP XR
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0097	Human Adult Heart, subtracted	Human Adult Heart	Heart			pBluescript
H0100	Human Whole Six Week Old Embryo	Human Whole Six Week Old Embryo	Embryo			Uni-ZAP XR
H0105	Human Fetal Heart, subtracted	Human Fetal Heart	Heart			pBluescript

H0107	Human Infant Adrenal Gland, subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0110	Human Old Ovary, subtracted	Human Old Ovary	Ovary			pBluescript
H0118	Human Adult Kidney	Human Adult Kidney	Kidney			Uni-ZAP XR
H0123	Human Fetal Dura Mater	Human Fetal Dura Mater	Brain			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarcoma	Sk Muscle		disease	Uni-ZAP XR
H0125	Cem cells cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0134	Raji Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0136	Supt Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0150	Human Epididymus	Epididymis	Testis			Uni-ZAP XR
H0156	Human Adrenal Gland Tumor	Human Adrenal Gland Tumor	Adrenal Gland		disease	Uni-ZAP XR
H0159	Activated T-Cells, 8 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0160	Activated T-Cells, 12 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0163	Human Synovium	Human Synovium	Synovium			Uni-ZAP XR
H0165	Human Prostate Cancer, Stage B2	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0166	Human Prostate Cancer, Stage B2 fraction	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0169	Human Prostate Cancer, Stage C fraction	Human Prostate Cancer, stage C	Prostate		disease	Uni-ZAP XR

H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage Human, II	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0176	CAMA1Ee Cell Line	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0179	Human Neutrophil	Human Neutrophil	Blood	Cell Line		Uni-ZAP XR
H0181	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0182	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0185	Activated T-Cell labeled with 4-thioluri	T-Cells	Blood	Cell Line		Lambda ZAP II
H0188	Human Normal Breast	Human Normal Breast	Breast			Uni-ZAP XR
H0196	Human Cardiomyopathy, subtracted	Human Cardiomyopathy	Heart			Uni-ZAP XR
H0208	Early Stage Human Lung, subtracted	Human Fetal Lung	Lung			pBluescript
H0212	Human Prostate, subtracted	Human Prostate	Prostate			pBluescript
H0213	Human Pituitary, subtracted	Human Pituitary				Uni-ZAP XR
H0214	Raji cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		pBluescript
H0224	Activated T-Cells, 12 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0225	Activated T-Cells, 12hrs, differentially expressed	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0231	Human Colon, subtraction	Human Colon				pBluescript
H0232	Human Colon, differential expression	Human Colon				pBluescript
H0234	human colon cancer, metastatic to liver, differentially expressed	Human Colon Cancer, metasticized to liver	Liver			pBluescript
H0242	Human Fetal Heart,	Human Fetal Heart	Heart			pBluescript

	Differential (Fetal-Specific)						
H0244	Human 8 Week Whole Embryo, subtracted	Human 8 Week Old Embryo	Embryo				Uni-ZAP XR
H0250	Human Activated Monocytes	Human Monocytes					Uni-ZAP XR
H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage		disease		Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone		disease		Uni-ZAP XR
H0253	Human adult testis, large inserts	Human Adult Testis	Testis				Uni-ZAP XR
H0254	Breast Lymph node cDNA library	Breast Lymph Node	Lymph Node				Uni-ZAP XR
H0255	breast lymph node CDNA library	Breast Lymph Node	Lymph Node				Lambda ZAP II
H0256	HL-60, unstimulated	Human HL-60 Cells, unstimulated	Blood	Cell Line			Uni-ZAP XR
H0257	HL-60, PMA 4H	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line			Uni-ZAP XR
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain				Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon		disease		Lambda ZAP II
H0264	human tonsils	Human Tonsil	Tonsil				Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood	Cell Line			Uni-ZAP XR
H0266	Human Microvascular Endothelial Cells, fract. A	HMEC	Vein	Cell Line			Lambda ZAP II
H0268	Human Umbilical Vein Endothelial Cells, fract. A	HUVE Cells	Umbilical vein	Cell Line			Lambda ZAP II
H0269	Human Umbilical Vein Endothelial Cells, fract. B	HUVE Cells	Umbilical vein	Cell Line			Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas				Uni-ZAP XR
H0271	Human Neutrophil,	Human Neutrophil -	Blood	Cell Line			Uni-ZAP XR

	Activated	Activated				
H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0275	Human Infant Adrenal Gland, Subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0280	K562 + PMA (36 hrs)	K562 Cell line	cell line	Cell Line		ZAP Express
H0284	Human OB MG63 control fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0286	Human OB MG63 treated (10 nM E2) fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0292	Human OB HOS treated (10 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0294	Amniotic Cells - TNF induced	Amniotic Cells - TNF induced	Placenta	Cell Line		Uni-ZAP XR
H0295	Amniotic Cells - Primary Culture	Amniotic Cells - Primary Culture	Placenta	Cell Line		Uni-ZAP XR
H0298	HCBB"s differential consolidation	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0300	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0305	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0306	CD34 depleted Buffy Coat (Cord Blood)	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0309	Human Chronic Synovitis	Synovium, Chronic Synovitis/ Osteoarthritis	Synovium		disease	Uni-ZAP XR
H0318	HUMAN B CELL LYMPHOMA	Human B Cell Lymphoma	Lymph Node		disease	Uni-ZAP XR
H0320	Human frontal cortex	Human Frontal Cortex	Brain			Uni-ZAP XR
H0327	human corpus colosum	Human Corpus Callosum	Brain			Uni-ZAP XR

H0328	human ovarian cancer	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0331	Hepatocellular Tumor	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0333	Hemangiopericytoma	Hemangiopericytoma	Blood vessel		disease	Lambda ZAP II
H0341	Bone Marrow Cell Line (RS4;11)	Bone Marrow Cell Line RS4;11	Bone Marrow	Cell Line		Uni-ZAP XR
H0343	stomach cancer (human)	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0351	Glioblastoma	Glioblastoma	Brain		disease	Uni-ZAP XR
H0352	wilm"s tumor	Wilm's Tumor			disease	Uni-ZAP XR
H0355	Human Liver	Human Liver, normal Adult				pCMVSport 1
H0359	KMH2 cell line	KMH2				ZAP Express
H0365	Osteoclastoma-normalized B	Human Osteoclastoma			disease	Uni-ZAP XR
H0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease	Uni-ZAP XR
H0372	Human Testes	Human Testes	Testis			pCMVSport 1
H0373	Human Heart	Human Adult Heart	Heart			pCMVSport 1
H0375	Human Lung	Human Lung				pCMVSport 1
H0376	Human Spleen	Human Adult Spleen	Spleen			pCMVSport 1
H0383	Human Prostate BPH, re-excision	Human Prostate BPH				Uni-ZAP XR
H0388	Human Rejected Kidney, 704 re-excision	Human Rejected Kidney			disease	pBluescript
H0391	H. Meningima, M6	Human Meningima	brain			pSport1
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0399	Human Kidney Cortex, re-rescue	Human Kidney Cortex				Lambda ZAP II
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0405	Human Pituitary, subtracted VI	Human Pituitary				pBluescript
H0409	H. Striatum Depression,	Human Brain,	Brain			pBluescript

	subtracted	Striatum Depression				
H0410	H. Male bladder, adult	H Male Bladder, Adult	Bladder			pSport1
H0411	H Female Bladder, Adult	Human Female Adult Bladder	Bladder			pSport1
H0412	Human umbilical vein endothelial cells, IL-4 induced	HUVE Cells	Umbilical vein	Cell Line		pSport1
H0413	Human Umbilical Vein Endothelial Cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		pSport1
H0415	H. Ovarian Tumor, II, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pCMVSport 2.0
H0417	Human Pituitary, subtracted VIII	Human Pituitary				pBluescript
H0418	Human Pituitary, subtracted VII	Human Pituitary				pBluescript
H0421	Human Bone Marrow, re-excision	Bone Marrow				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSport1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSport1
H0424	Human Pituitary, subt IX	Human Pituitary				pBluescript
H0427	Human Adipose	Human Adipose, left hiplipoma				pSport1
H0428	Human Ovary	Human Ovary Tumor	Ovary			pSport1
H0431	H. Kidney Medulla, re-excision	Kidney medulla	Kidney			pBluescript
H0433	Human Umbilical Vein Endothelial cells, frac B, re-excision	HUVE Cells	Umbilical vein	Cell Line		pBluescript
H0435	Ovarian Tumor 10-3-95	Ovarian Tumor, OV350721	Ovary			pCMVSport 2.0
H0436	Resting T-Cell Library,II	T-Cells	Blood	Cell Line		pSport1
H0437	H Umbilical Vein Endothelial Cells, frac A, re-excision	HUVE Cells	Umbilical vein	Cell Line		Lambda ZAP II

H0438	H. Whole Brain #2, re-excision	Human Whole Brain #2				ZAP Express
H0439	Human Eosinophils	Eosinophils				pBluescript
H0440	FGF enriched mixed library	Mixed libraries				pCMVSport 1
H0441	H. Kidney Cortex, subtracted	Kidney cortex	Kidney			pBluescript
H0442	H. Striatum Depression, subt II	Human Brain, Striatum Depression	Brain			pBluescript
H0444	Spleen metastic melanoma	Spleen, Metastic malignant melanoma	Spleen		disease	pSport1
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSport1
H0453	H. Kidney Pyramid, subtracted	Kidney pyramids	Kidney			pBluescript
H0455	H. Striatum Depression, subt	Human Brain, Striatum Depression	Brain			pBluescript
H0457	Human Eosinophils	Human Eosinophils				pSport1
H0461	H. Kidney Medulla, subtracted	Kidney medulla	Kidney			pBluescript
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSport1
H0483	Breast Cancer cell line, MDA 36	Breast Cancer Cell line, MDA 36				pSport1
H0484	Breast Cancer Cell line, angiogenic	Breast Cancer Cell line, Angiogenic, 36T3				pSport1
H0485	Hodgkin"s Lymphoma I	Hodgkin"s Lymphoma I			disease	pCMVSport 2.0
H0486	Hodgkin"s Lymphoma II	Hodgkin"s Lymphoma II			disease	pCMVSport 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSport 2.0
H0490	HI-60, untreated, subtracted	Human HL-60 Cells, unstimulated	Blood	Cell Line		Uni-ZAP XR
H0494	Keratinocyte	Keratinocyte				pCMVSport 2.0
H0497	HEL cell line	HEL cell line		HEL		pSport1

				92.1.7			
H0506	Ulcerative Colitis	Colon	Colon				pSport1
H0509	Liver, Hepatoma	Human Liver, Hepatoma, patient 8	Liver		disease		pCMVSport 3.0
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver				pCMVSport 3.0
H0518	pBMC stimulated w/ poly I/C	pBMC stimulated with poly I/C					pCMVSport 3.0
H0519	NTERA2, control	NTERA2, Teratocarcinoma cell line					pCMVSport 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line					pSport1
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells					pCMVSport 3.0
H0522	Primary Dendritic cells,frac 2	Primary Dendritic cells					pCMVSport 3.0
H0525	PCR, pBMC I/C treated	pBMC stimulated with poly I/C					PCRII
H0529	Myoloid Progenitor Cell Line	TF-1 Cell Line; Myoloid progenitor cell line					pCMVSport 3.0
H0530	Human Dermal Endothelial Cells,untreated	Human Dermal Endothelial Cells; untreated					pSport1
H0537	H. Primary Dendritic Cells,lib 3	Primary Dendritic cells					pCMVSport 2.0
H0538	Merkel Cells	Merkel cells	Lymph node				pSport1
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas		disease		pSport1
H0540	Skin, burned	Skin, leg burned	Skin				pSport1
H0542	T Cell helper I	Helper T cell					pCMVSport 3.0
H0543	T cell helper II	Helper T cell					pCMVSport 3.0
H0544	Human endometrial stromal cells	Human endometrial stromal cells					pCMVSport 3.0
H0545	Human endometrial	Human endometrial					pCMVSport 3.0

	stromal cells-treated with progesterone	stromal cells-treated with proge				
H0546	Human endometrial stromal cells-treated with estradiol	Human endometrial stromal cells-treated with estra				pCMVSport 3.0
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	NTERA2, Teratocarcinoma cell line				pSport1
H0549	H. Epididymus, caput & corpus	Human Epididymus, caput and corpus				Uni-ZAP XR
H0550	H. Epididymus, cauda	Human Epididymus, cauda				Uni-ZAP XR
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSport 3.0
H0553	Human Placenta	Human Placenta				pCMVSport 3.0
H0555	Rejected Kidney, lib 4	Human Rejected Kidney	Kidney		disease	pCMVSport 3.0
H0556	Activated T-cell(12h)/Thiouridine-re-excision	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0559	HL-60, PMA 4H, re-excision	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line		Uni-ZAP XR
H0560	KMH2	KMH2				pCMVSport 3.0
H0561	L428	L428				pCMVSport 3.0
H0563	Human Fetal Brain, normalized 50021F	Human Fetal Brain				pCMVSport 2.0
H0566	Human Fetal Brain,normalized c50F	Human Fetal Brain				pCMVSport 2.0
H0569	Human Fetal Brain, normalized CO	Human Fetal Brain				pCMVSport 2.0
H0570	Human Fetal Brain, normalized C500H	Human Fetal Brain				pCMVSport 2.0
H0571	Human Fetal Brain, normalized C500HE	Human Fetal Brain				pCMVSport 2.0
H0574	Hepatocellular Tumor, re-excision	Hepatocellular Tumor	Liver		disease	Lambda ZAP II

H0575	Human Adult Pulmonary;re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0576	Resting T-Cell; re-excision	T-Cells	Blood	Cell Line		Lambda ZAP II
H0578	Human Fetal Thymus	Fetal Thymus	Thymus			pSport1
H0579	Pericardium	Pericardium	Heart			pSport1
H0580	Dendritic cells, pooled	Pooled dendritic cells				pCMVSport 3.0
H0581	Human Bone Marrow, treated	Human Bone Marrow	Bone Marrow			pCMVSport 3.0
H0583	B Cell lymphoma	B Cell Lymphoma	B Cell		disease	pCMVSport 3.0
H0584	Activated T-cells, 24 hrs,re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0586	Healing groin wound, 6.5 hours post incision	healing groin wound, 6.5 hours post incision - 2/	groin		disease	pCMVSport 3.0
H0587	Healing groin wound; 7.5 hours post incision	Groin-2/19/97	groin		disease	pCMVSport 3.0
H0590	Human adult small intestine,re-excision	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0591	Human T-cell lymphoma;re-excision	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0592	Healing groin wound - zero hr post-incision (control)	HGS wound healing project; abdomen			disease	pCMVSport 3.0
H0593	Olfactory epithelium;nasalcavity	Olfactory epithelium from roof of left nasal cacit				pCMVSport 3.0
H0594	Human Lung Cancer;re-excision	Human Lung Cancer	Lung		disease	Lambda ZAP II
H0595	Stomach cancer (human);re-excision	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0596	Human Colon Cancer;re-excision	Human Colon Cancer	Colon			Lambda ZAP II
H0597	Human Colon; re-excision	Human Colon				Lambda ZAP II
H0599	Human Adult Heart;re-excision	Human Adult Heart	Heart			Uni-ZAP XR

H0600	Healing Abdomen wound;70&90 min post incision	Abdomen			disease	pCMVSport 3.0
H0604	Human Pituitary, re-excision	Human Pituitary				pBluescript
H0606	Human Primary Breast Cancer;re-excision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0607	H.Leukocytes, normalized cot 50A3	H.Leukocytes				pCMVSport 1
H0613	H.Leukocytes, normalized cot 5B	H.Leukocytes				pCMVSport 1
H0615	Human Ovarian Cancer Reexcision	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0616	Human Testes, Reexcision	Human Testes	Testis			Uni-ZAP XR
H0617	Human Primary Breast Cancer Reexcision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0618	Human Adult Testes, Large Inserts, Reexcision	Human Adult Testis	Testis			Uni-ZAP XR
H0619	Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0620	Human Fetal Kidney; Reexcision	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0622	Human Pancreas Tumor; Reexcision	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0624	12 Week Early Stage Human II; Reexcision	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0625	Ku 812F Basophils Line	Ku 812F Basophils				pSport1
H0628	Human Pre-Differentiated Adipocytes	Human Pre-Differentiated Adipocytes				Uni-ZAP XR
H0631	Saos2, Dexamethosome Treated	Saos2 Cell Line; Dexamethosome Treated				pSport1
H0632	Hepatocellular Tumor;re-excision	Hepatocellular Tumor	Liver			Lambda ZAP II

H0633	Lung Carcinoma A549 TNFalpha activated	TNFalpha activated A549--Lung Carcinoma			disease	pSport1
H0634	Human Testes Tumor, re-excision	Human Testes Tumor	Testis		disease	Uni-ZAP XR
H0635	Human Activated T-Cells, re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0637	Dendritic Cells From CD34 Cells	Dentritic cells from CD34 cells				pSport1
H0638	CD40 activated monocyte dendridic cells	CD40 activated monocyte dendridic cells				pSport1
H0640	Ficolled Human Stromal Cells, Untreated	Ficolled Human Stromal Cells, Untreated				Other
H0641	LPS activated derived dendritic cells	LPS activated monocyte derived dendritic cells				pSport1
H0643	Hep G2 Cells, PCR library	Hep G2 Cells				Other
H0644	Human Placenta (re-excision)	Human Placenta	Placenta			Uni-ZAP XR
H0645	Fetal Heart, re-excision	Human Fetal Heart	Heart			Uni-ZAP XR
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,	Metastatic squamous cell lung carcinoma, poorly di				pSport1
H0647	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	Invasive poorly differentiated lung adenocarcinoma			disease	pSport1
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	Papillary Cstic neoplasm of low malignant potentia			disease	pSport1
H0649	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0650	B-Cells	B-Cells				pCMVSport 3.0

H0651	Ovary, Normal: (9805C040R)	Normal Ovary				pSport1
H0652	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0653	Stromal Cells	Stromal Cells				pSport1
H0656	B-cells (unstimulated)	B-cells (unstimulated)				pSport1
H0657	B-cells (stimulated)	B-cells (stimulated)				pSport1
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	9809C332- Poorly differentiate	Ovary & Fallopian Tubes		disease	pSport1
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	Grade II Papillary Carcinoma, Ovary	Ovary		disease	pSport1
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	Poorly differentiated carcinoma, ovary			disease	pSport1
H0661	Breast, Cancer: (4004943 A5)	Breast cancer			disease	pSport1
H0662	Breast, Normal: (4005522B2)	Normal Breast - #4005522(B2)	Breast			pSport1
H0663	Breast, Cancer: (4005522 A2)	Breast Cancer - #4005522(A2)	Breast		disease	pSport1
H0664	Breast, Cancer: (9806C012R)	Breast Cancer	Breast		disease	pSport1
H0665	Stromal cells 3.88	Stromal cells 3.88				pSport1
H0667	Stromal cells(HBM3.18)	Stromal cell(HBM 3.18)				pSport1
H0668	stromal cell clone 2.5	stromal cell clone 2.5				pSport1
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	Ovarian Cancer - 4004650A3				pSport1
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576A8)	Ovary			pSport1

H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate			Uni-ZAP XR
H0674	Human Prostate Cancer, Stage C; re-excission	Human Prostate Cancer, stage C	Prostate			Uni-ZAP XR
H0682	Serous Papillary Adenocarcinoma	serous papillary adenocarcinoma (9606G304SPA3B)				pCMVSport 3.0
H0683	Ovarian Serous Papillary Adenocarcinoma	Serous papillary adenocarcinoma, stage 3C (9804G01				pCMVSport 3.0
H0684	Serous Papillary Adenocarcinoma	Ovarian Cancer-9810G606	Ovaries			pCMVSport 3.0
H0685	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-				pCMVSport 3.0
H0686	Adenocarcinoma of Ovary, Human Cell Line	Adenocarcinoma of Ovary, Human Cell Line, # SW-626				pCMVSport 3.0
H0687	Human normal ovary(#9610G215)	Human normal ovary(#9610G215)	Ovary			pCMVSport 3.0
H0688	Human Ovarian Cancer(#9807G017)	Human Ovarian cancer(#9807G017), mRNA from Maura Ru				pCMVSport 3.0
H0689	Ovarian Cancer	Ovarian Cancer, #9806G019				pCMVSport 3.0
H0690	Ovarian Cancer, # 9702G001	Ovarian Cancer, #9702G001				pCMVSport 3.0
H0694	Prostate gland adenocarcinoma	Prostate gland, adenocarcinoma, mod/diff, gleason	prostate gland			pCMVSport 3.0
H0695	mononucleocytes from patient	mononucleocytes from patient at Shady Grove Hospit				pCMVSport 3.0
N0006	Human Fetal Brain	Human Fetal Brain				
S0001	Brain frontal cortex	Brain frontal cortex	Brain			Lambda ZAP II
S0002	Monocyte activated	Monocyte-activated	blood	Cell Line		Uni-ZAP XR

S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0007	Early Stage Human Brain	Human Fetal Brain				Uni-ZAP XR
S0010	Human Amygdala	Amygdala				Uni-ZAP XR
S0011	STROMAL - OSTEOCLASTOMA	Osteoclastoma	bone		disease	Uni-ZAP XR
S0013	Prostate	Prostate	prostate			Uni-ZAP XR
S0015	Kidney medulla	Kidney medulla	Kidney			Uni-ZAP XR
S0016	Kidney Pyramids	Kidney pyramids	Kidney			Uni-ZAP XR
S0022	Human Osteoclastoma Stromal Cells - unamplified	Osteoclastoma Stromal Cells				Uni-ZAP XR
S0026	Stromal cell TF274	stromal cell	Bone marrow	Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0028	Smooth muscle,control	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0029	brain stem	Brain stem	brain			Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord			Uni-ZAP XR
S0032	Smooth muscle-ILb induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0036	Human Substantia Nigra	Human Substantia Nigra				Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	Human Whole Brain #2				ZAP Express
S0040	Adipocytes	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0044	Prostate BPH	prostate BPH	Prostate		disease	Uni-ZAP XR
S0045	Endothelial cells-control	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0046	Endothelial-induced	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0049	Human Brain, Striatum	Human Brain, Striatum				Uni-ZAP XR
S0050	Human Frontal Cortex, Schizophrenia	Human Frontal Cortex,			disease	Uni-ZAP XR

		Schizophrenia			disease	
S0051	Human Hypothalmus,Schizophrenia	Human Hypothalamus, Schizophrenia				Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0112	Hypothalamus		Brain			Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0116	Bone marrow	Bone marrow	Bone marrow			Uni-ZAP XR
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0132	Epithelial-TNFa and INF induced	Airway Epithelial				Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0140	eosinophil-IL5 induced	eosinophil	lung	Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF treated)	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0146	prostate-edited	prostate BPH	Prostate			Uni-ZAP XR
S0150	LNCAP prostate cell line	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
S0152	PC3 Prostate cell line	PC3 prostate cell line				Uni-ZAP XR
S0182	Human B Cell 8866	Human B- Cell 8866				Uni-ZAP XR
S0190	Prostate BPH,Lib 2, subtracted	Human Prostate BPH				pSport1
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0206	Smooth Muscle- HASTE normalized	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S0208	Messangial cell, frac 1	Messangial cell				pSport1
S0210	Messangial cell, frac 2	Messangial cell				pSport1
S0212	Bone Marrow Stromal	Bone Marrow				pSport1

	Cell, untreated	Stromal Cell,untreated				
S0214	Human Osteoclastoma, re-excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0218	Apoptotic T-cell, re-excision	apoptotic cells		Cell Line		Uni-ZAP XR
S0222	H. Frontal cortex,epileptic;re-excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (Il1/TNF), subt	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMVSport 2.0
S0260	Spinal Cord, re-excision	Spinal cord	spinal cord			Uni-ZAP XR
S0276	Synovial hypoxia-RSF subtracted	Synovial fobroblasts (rheumatoid)	Synovial tissue			pSport1
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0282	Brain Frontal Cortex, re-excision	Brain frontal cortex	Brain			Lambda ZAP II
S0292	Osteoarthritis (OA-4)	Human Osteoarthritic Cartilage	Bone		disease	pSport1
S0298	Bone marrow stroma,treated	Bone marrow stroma,treatedSB	Bone marrow			pSport1
S0300	Frontal lobe,dementia;re-excision	Frontal Lobe dementia/Alzheimer's	Brain			Uni-ZAP XR
S0308	Spleen/normal	Spleen normal				pSport1
S0318	Human Normal Cartilage Fraction II	Human Normal Cartilage				pSport1
S0328	Palate carcinoma	Palate carcinoma	Uvula		disease	pSport1
S0330	Palate normal	Palate normal	Uvula			pSport1
S0332	Pharynx carcinoma	Pharynx carcinoma	Hypopharynx			pSport1
S0334	Human Normal Cartilage Fraction III	Human Normal Cartilage				pSport1

S0338	Human Osteoarthritic Cartilage Fraction III	Human osteoarthritic cartilage			disease	pSport1
S0342	Adipocytes;re-excision	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0344	Macrophage-oxLDL; re-excision	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0346	Human Amygdala;re-excision	Amygdala				Uni-ZAP XR
S0350	Pharynx Carcinoma	Pharynx carcinoma	Hypopharynx		disease	pSport1
S0352	Larynx Carcinoma	Larynx carcinoma			disease	pSport1
S0354	Colon Normal II	Colon Normal	Colon			pSport1
S0356	Colon Carcinoma	Colon Carcinoma	Colon		disease	pSport1
S0358	Colon Normal III	Colon Normal	Colon			pSport1
S0360	Colon Tumor II	Colon Tumor	Colon		disease	pSport1
S0364	Human Quadriceps	Quadriceps muscle				pSport1
S0366	Human Soleus	Soleus Muscle				pSport1
S0370	Larynx carcinoma II	Larynx carcinoma			disease	pSport1
S0374	Normal colon	Normal colon				pSport1
S0376	Colon Tumor	Colon Tumor			disease	pSport1
S0378	Pancreas normal PCA4 No	Pancreas Normal PCA4 No				pSport1
S0380	Pancreas Tumor PCA4 Tu	Pancreas Tumor PCA4 Tu			disease	pSport1
S0384	Tongue carcinoma	Tongue carcinoma			disease	pSport1
S0386	Human Whole Brain, re-excision	Whole brain	Brain			ZAP Express
S0388	Human Hypothalamus,schizophrenia, re-excision	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0390	Smooth muscle, control; re-excision	Smooth muscle	Pulmanary artery	Cell Line		Uni-ZAP XR
S0392	Salivary Gland	Salivary gland; normal				pSport1
S0404	Rectum normal	Rectum, normal				pSport1
S0406	Rectum tumour	Rectum tumour				pSport1

S0408	Colon, normal	Colon, normal				pSport1
S0410	Colon, tumour	Colon, tumour				pSport1
S0412	Temporal cortex-Alzheizmer; subtracted	Temporal cortex, alzheimer			disease	Other
S0414	Hippocampus, Alzheimer Subtracted	Hippocampus, Alzheimer Subtracted				Other
S0418	CHME Cell Line;treated 5 hrs	CHME Cell Line; treated				pCMVSport 3.0
S0420	CHME Cell Line,untreated	CHME Cell line, untreatetd				pSport1
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)	Mo7e Cell Line GM-CSF treated (1ng/ml)				pCMVSport 3.0
S0424	TF-1 Cell Line GM-CSF Treated	TF-1 Cell Line GM-CSF Treated				pSport1
S0426	Monocyte activated; re-excision	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0428	Neutrophils control; re-excision	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0430	Aryepiglottis Normal	Aryepiglottis Normal				pSport1
S0432	Sinus piniformis Tumour	Sinus piniformis Tumour				pSport1
S0434	Stomach Normal	Stomach Normal			disease	pSport1
S0436	Stomach Tumour	Stomach Tumour			disease	pSport1
S0438	Liver Normal Met5No	Liver Normal Met5No				pSport1
S0440	Liver Tumour Met 5 Tu	Liver Tumour				pSport1
S0442	Colon Normal	Colon Normal				pSport1
S0444	Colon Tumor	Colon Tumour			disease	pSport1
S0448	Larynx Normal	Larynx Normal				pSport1
S0458	Thyroid Normal (SDCA2 No)	Thyroid normal				pSport1
S0460	Thyroid Tumour	Thyroid Tumour				pSport1
S0462	Thyroid Thyroiditis	Thyroid Thyroiditis				pSport1
S0474	Human blood platelets	Platelets	Blood			Other

			platelets			
S3012	Smooth Muscle Serum Treated, Norm	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S3014	Smooth muscle, serum induced,re-exc	Smooth muscle	Pulmanary artery	Cell Line		pBluescript
S6014	H. hypothalamus, frac A	Hypothalamus	Brain			ZAP Express
S6016	H. Frontal Cortex, Epileptic	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S6022	H. Adipose Tissue	Human Adipose Tissue				Uni-ZAP XR
S6024	Alzheimers, spongy change	Alzheimer"s/Spongy change	Brain		disease	Uni-ZAP XR
S6026	Frontal Lobe, Dementia	Frontal Lobe dementia/Alzheimer's	Brain			Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		disease	Uni-ZAP XR
T0002	Activated T-cells	Activated T-Cell, PBL fraction	Blood	Cell Line		pBluescript SK-
T0004	Human White Fat	Human White Fat				pBluescript SK-
T0006	Human Pineal Gland	Human Pinneal Gland				pBluescript SK-
T0008	Colorectal Tumor	Colorectal Tumor			disease	pBluescript SK-
T0010	Human Infant Brain	Human Infant Brain				Other
T0023	Human Pancreatic Carcinoma	Human Pancreatic Carcinoma			disease	pBluescript SK-
T0039	HSA 172 Cells	Human HSA172 cell line				pBluescript SK-
T0040	HSC172 cells	SA172 Cells				pBluescript SK-
T0041	Jurkat T-cell G1 phase	Jurkat T-cell				pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line				pBluescript SK-
T0048	Human Aortic Endothelium	Human Aortic Endothilium				pBluescript SK-
T0049	Aorta endothelial cells + TNF-a	Aorta endothelial cells				pBluescript SK-
T0060	Human White Adipose	Human White Fat				pBluescript SK-
T0067	Human Thyroid	Human Thyroid				pBluescript SK-

T0069	Human Uterus, normal	Human Uterus, normal				pBluescript SK-
T0071	Human Bone Marrow	Human Bone Marrow				pBluescript SK-
T0082	Human Adult Retina	Human Adult Retina				pBluescript SK-
T0103	Human colon carcinoma (HCC) cell line					pBluescript SK-
T0109	Human (HCC) cell line liver (mouse) metastasis, remake					pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake					pBluescript SK-
T0112	Human (Caco-2) cell line, adenocarcinoma, colon					pBluescript SK-
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake					pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line					pBluescript SK-
L0002	Atrium cDNA library Human heart					
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0021	Human adult (K.Okubo)					
L0022	Human adult lung 3" directed MboI cDNA					
L0045	Human keratinocyte differential display (B.Lin)					
L0055	Human promyelocyte					
L0065	Liver HepG2 cell line.					
L0105	Human aorta polyA+ (TFujiwara)	aorta				
L0142	Human placenta cDNA (TFujiwara)	placenta				
L0157	Human fetal brain (TFujiwara)		brain			

L0163	Human heart cDNA (YNakamura)		heart			
L0185	Human immortalized fibroblasts (H.L.Ozer)			HS74 and its SV40-transformed sublines		
L0194	Human pancreatic cancer cell line Patu 8988t	pancreatic cancer		Patu 8988t		
L0351	Infant brain, Bento Soares					BA, M13-derived
L0352	Normalized infant brain, Bento Soares					BA, M13-derived
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0364	NCI_CGAP_GC5	germ cell tumor				Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-
L0367	NCI_CGAP_Sch1	Schwannoma tumor				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0371	NCI_CGAP_Br3	breast tumor	breast			Bluescript SK-
L0372	NCI_CGAP_Co12	colon tumor	colon			Bluescript SK-
L0373	NCI_CGAP_Co11	tumor	colon			Bluescript SK-
L0374	NCI_CGAP_Co2	tumor	colon			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0378	NCI_CGAP_Lu1	lung tumor	lung			Bluescript SK-
L0379	NCI_CGAP_Lym3	lymphoma	lymph node			Bluescript SK-
L0381	NCI_CGAP_HN4	squamous cell carcinoma	pharynx			Bluescript SK-
L0382	NCI_CGAP_Pr25	epithelium (cell line)	prostate			Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate			Bluescript SK-
L0388	NCI_CGAP_HN6	normal gingiva (cell line from immortalized kerati				Bluescript SK-
L0435	Infant brain, LLNL array					lafmid BA

	of Dr. M. Soares INIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			
L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0448	3HFLSK20					Lafmid K
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0456	Human retina cDNA Tsp509I-cleaved sublibrary	retina	eye			lambda gt10
L0470	BL29 Burkitt's lymphoma, Pascalis Sideras					lambda ZAP 2
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0481	CD34+DIRECTIONAL					Lambda ZAPII
L0483	Human pancreatic islet					Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle			Lambda ZAPII
L0493	NCI_CGAP_Ov26	papillary serous carcinoma	ovary			pAMP1
L0506	NCI_CGAP_Br16	lobullar carcinoma in situ	breast			pAMP1
L0512	NCI_CGAP_Ov36	borderline ovarian carcinoma	ovary			pAMP1
L0515	NCI_CGAP_Ov32	papillary serous carcinoma	ovary			pAMP1
L0517	NCI_CGAP_Pr1					pAMP10
L0518	NCI_CGAP_Pr2					pAMP10
L0519	NCI_CGAP_Pr3					pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI_CGAP_Ew1	Ewing"s sarcoma				pAMP10
L0526	NCI_CGAP_Pr12	metastatic prostate bone lesion				pAMP10

L0527	NCI_CGAP_Ov2	ovary				pAMP10
L0528	NCI_CGAP_Pr5	prostate				pAMP10
L0529	NCI_CGAP_Pr6	prostate				pAMP10
L0530	NCI_CGAP_Pr8	prostate				pAMP10
L0532	NCI_CGAP_Thy1	thyroid				pAMP10
L0534	Chromosome 7 Fetal Brain cDNA Library	brain	brain			pAMP10
L0536	NCI_CGAP_Br4	normal ductal tissue	breast			pAMP10
L0540	NCI_CGAP_Pr10	invasive prostate tumor	prostate			pAMP10
L0542	NCI_CGAP_Pr11	normal prostatic epithelial cells	prostate			pAMP10
L0545	NCI_CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0561	NCI_CGAP_HN11	normal squamous epithelium	tongue			pAMP10
L0564	Jia bone marrow stroma	bone marrow stroma				pBluescript
L0565	Normal Human Trabecular Bone Cells	Bone	Hip			pBluescript
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0584	Stratagene cDNA library Human heart, cat#936208					pBluescript SK(+)
L0587	Stratagene colon HT29 (#937221)					pBluescript SK-
L0588	Stratagene endothelial cell 937223					pBluescript SK-
L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-

L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain			pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0597	Stratagene corneal stroma (#937222)		cornea			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0607	NCI_CGAP_Lym6	mantle cell lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0611	Schiller meningioma	meningioma	brain			pBluescript SK- (Stratagene)
L0615	22 week old human fetal liver cDNA library					pBluescriptII SK(-)
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0631	NCI_CGAP_Br7		breast			pCMV-SPORT4
L0635	NCI_CGAP_PNS1	dorsal root ganglion	peripheral nervous system			pCMV-SPORT4
L0636	NCI_CGAP_Pit1	four pooled pituitary adenomas	brain			pCMV-SPORT6
L0637	NCI_CGAP_Brn53	three pooled meningiomas	brain			pCMV-SPORT6

L0638	NCI_CGAP_Brn35	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0640	NCI_CGAP_Br18	four pooled high-grade tumors, including two prima	breast			pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa tumor	colon			pCMV-SPORT6
L0643	NCI_CGAP_Co19	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately-differentiated adenocarcinoma	colon			pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue			pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus			pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high-grade transitional cell tumors	genitourinary tract			pCMV-SPORT6
L0650	NCI_CGAP_Kid13	2 pooled Wilms" tumors, one primary and one metast	kidney			pCMV-SPORT6
L0651	NCI_CGAP_Kid8	renal cell tumor	kidney			pCMV-SPORT6
L0652	NCI_CGAP_Lu27	four pooled poorly-differentiated adenocarcinomas	lung			pCMV-SPORT6
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0654	NCI_CGAP_Lu31		lung, cell line			pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6

L0656	NCI_CGAP_Ov38	normal epithelium	ovary			pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma, metastatic to lymph node	skin			pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcino	uterus			pCMV-SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma,	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood			pCMV-SPORT6
L0698	Testis 2					PGEM 5zf(+)
L0717	Gessler Wilms tumor					pSPORT1
L0731	Soares_pregnant_uterus_NbHPU		uterus			pT7T3-Pac
L0738	Human colorectal cancer					pT7T3D
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified

L0741	Soares adult brain N2b4HB55Y		brain				pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain				pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast				pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst		breast				pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye				pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye				pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbHH 19W		heart				pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen				pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_spleen _1NFLS_S1		Liver and Spleen				pT7T3D (Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_NbHL1		lung				pT7T3D

	9W						(Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary				pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor_NbHPA	parathyroid tumor	parathyroid gland				pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N3HPG		pineal gland				pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta				pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9weeks_2NbHP8to9W		placenta				pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_sclerosis_2NbHMSP	multiple sclerosis lesions					pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibroblasts_NbHSF	senescent fibroblast					pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT						pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares total fetus Nb2H						pT7T3D-Pac

	F8_9w					(Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic lymphotic leukemia				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0762	NCI_CGAP_Br1.1	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0765	NCI_CGAP_Co4	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0767	NCI_CGAP_GC3	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Bm25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified

L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S1		pooled				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9W_OT		pooled				pT7T3D-Pac

	_PA_P_S1					(Pharmacia) with a modified polylinker
L0782	NCI_CGAP_Pr21	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0785	Barstead spleen HPLRB2		spleen			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified

L0793	NCI_CGAP_Sub7						pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate				pT7T3D-Pac

L2251	Human fetal lung	Fetal lung					(Pharmacia) with a modified polylinker
L3904	NCI_CGAP_Brn64	glioblastoma with EGFR amplification	brain				pCMV-SPORT6
L4501	NCI_CGAP_Sub8						pT7T3D-Pac (Pharmacia) with a modified polylinker
L5564	NCI_CGAP_HN20		normal head/neck tissue				pAMP1
L5565	NCI_CGAP_Brn66	glioblastoma with probably TP53 mutation and witho	brain				pCMV-SPORT6
L5622	NCI_CGAP_Skn3		skin				pCMV-SPORT6

Table 5

OMIM Reference	Description
102772	[AMP deaminase deficiency, erythrocytic]
106210	Peters anomaly
106210	Cataract, congenital, with late-onset corneal dystrophy
106210	Foveal hypoplasia, isolated, 136520
106210	Aniridia
107271	CD59 deficiency
112262	Fibrodysplasia ossificans progressiva, 135100
114290	Campomelic dysplasia with autosomal sex reversal
114550	Hepatocellular carcinoma
115500	Acatalasemia
116860	Cavernous angiomatous malformations
121050	Contractural arachnodactyly, congenital
125270	Porphyria, acute hepatic
125270	Lead poisoning, susceptibility to
128100	Dystonia-1, torsion
129900	EEC syndrome-1
131400	Eosinophilia, familial
134570	Factor XIIIA deficiency
136530	Male infertility, familial
137350	Amyloidosis, Finnish type, 105120
138033	Diabetes mellitus, type II
138040	Cortisol resistance
148900	Klippel-Feil syndrome with laryngeal malformation

151390	Leukemia, acute T-cell
153455	Cutis laxa, recessive, type I, 219100
156845	Tietz syndrome, 103500
156845	Waardenburg syndrome, type IIA, 193510
156845	Waardenburg syndrome/ocular albinism, digenic, 103470
159000	Muscular dystrophy, limb-girdle, type 1A
162100	Neuralgic amyotrophy with predilection for brachial plexus
164500	Spinocerebellar ataxia-7
168450	Hypoparathyroidism, autosomal dominant
168450	Hypoparathyroidism, autosomal recessive
170500	Myotonia congenita, atypical acetazolamide-responsive
170500	Paramyotonia congenita, 168300
170500	Hyperkalemic periodic paralysis
179095	Male infertility
179615	Reticulosis, familial histiocytic, 267700
179615	Severe combined immunodeficiency, B cell-negative, 601457
179616	Severe combined immunodeficiency, B cell-negative, 601457
180385	Leukemia, acute T-cell
180860	Russell-Silver syndrome
181460	Schistosoma mansoni, susceptibility/resistance to
182600	Spastic paraplegia-3A
182870	Spherocytosis-1
182870	Elliptocytosis-3
182870	Anemia, neonatal hemolytic, fatal and near-fatal
191100	Tuberous sclerosis-1
192974	Neonatal alloimmune thrombocytopenia
192974	Glycoprotein Ia deficiency

194070	Wilms tumor, type 1
194070	Denys-Drash syndrome
194070	Frasier syndrome, 136680
203800	Alstrom syndrome
215700	Citrullinemia
216550	Cohen syndrome
223360	Dopamine-beta-hydroxylase deficiency
227646	Fanconi anemia, type D
233700	Chronic granulomatous disease due to deficiency of NCF-1
245349	Lacticacidemia due to PDX1 deficiency
253601	Miyoshi myopathy, 254130
253601	Muscular dystrophy, limb-girdle, type 2B
257200	Niemann-Pick disease, type A
257200	Niemann-Pick disease, type B
264470	Adrenoleukodystrophy, pseudoneonatal
268900	[Sarcosinemia]
300046	Mental retardation, X-linked 23, nonspecific
300047	Mental retardation, X-linked 20
300071	Night blindness, congenital stationary, type 2
300110	Night blindness, congenital stationary, X-linked incomplete, 300071
300123	Mental retardation with isolated growth hormone deficiency
300600	Ocular albinism, Forsius-Eriksson type
301000	Thrombocytopenia, X-linked, 313900
301000	Wiskott-Aldrich syndrome
301201	Amelogenesis imperfecta-3, hypoplastic type
301830	Arthrogryposis, X-linked (spinal muscular atrophy, infantile, X-linked)
301835	Arts syndrome

301845	Bazex syndrome
307150	Hypertrichosis, congenital generalized
309470	Mental retardation, X-linked, syndromic-3, with spastic diplegia
309500	Renpenning syndrome-1
309610	Mental retardation, X-linked, syndromic-2, with dysmorphism and cerebral atrophy
309850	Brunner syndrome
310490	Cowchock syndrome
311050	Optic atrophy, X-linked
311850	Phosphoribosyl pyrophosphate synthetase-related gout
312060	Properdin deficiency, X-linked
600079	Colon cancer
600151	Bardet-Biedl syndrome 3
600163	Long QT syndrome-3
600194	Ichthyosis bullosa of Siemens, 146800
600225	Phenylketonuria, atypical, due to GCH1 deficiency, 233910
600225	Dystonia, DOPA-responsive, 128230
600231	Palmoplantar keratoderma, Bothnia type
600281	Non-insulin-dependent diabetes mellitus, 125853
600281	MODY, type 1, 125850
600807	Bronchial asthma
601090	Iridogoniodysgenesis, 601631
601154	Cardiomyopathy, dilated, 1E
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601596	Charcot-Marie-Tooth neuropathy, demyelinating
601692	Reis-Bucklers corneal dystrophy
601692	Corneal dystrophy, Avellino type

601692	Corneal dystrophy, Groenouw type I, 121900
601692	Corneal dystrophy, lattice type I, 122200
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601850	Retinitis pigmentosa-deafness syndrome
602028	Multiple myeloma
602089	Hemangioma, capillary, hereditary
602092	Deafness, autosomal recessive 18
602121	Deafness, autosomal dominant nonsyndromic sensorineural, 1, 124900
602460	Deafness, autosomal dominant 15, 602459

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the secreted protein.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or a cDNA contained in ATCC deposit Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide encoded by the cDNA contained in ATCC deposit Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide sequence encoded by the cDNA contained in ATCC deposit Z are also encompassed by the invention.

Signal Sequences

The present invention also encompasses mature forms of the polypeptide having the polypeptide sequence of SEQ ID NO:Y and/or the polypeptide sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as,

for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretary leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1A.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence

shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as desribed below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X, the complementary strand thereto, and/or the cDNA sequence contained in a deposited clone.

The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y and/or encoded by a deposited clone.

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence contained in a deposited cDNA clone or the

complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited clone, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein).

Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, the polypeptide sequence encoded by the cDNA contained in a deposited clone, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein).

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1A, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the presence invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp.

App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the

deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, an amino acid sequences shown in Table 1A (SEQ ID NO:Y) or to the amino acid sequence encoded by cDNA contained in a deposited clone can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window

Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not

matched/aligned with the query sequnce are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over

3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification or (v) fusion of the polypeptide with another compound, such as albumin (including, but not limited to, recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the polynucleotides of the invention.

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence which: is a portion of that contained in a deposited clone, or encoding the polypeptide encoded by the cDNA in a deposited clone; is a portion of that shown in SEQ ID NO:X or the complementary strand thereto, or is a portion of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:Y. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt,

and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in a deposited clone or the nucleotide sequence shown in SEQ ID NO:X. In this context "about" includes the particularly recited value, a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40,

41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotides encoding these domains are also contemplated.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) polypeptide of invention protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an antibody to the polypeptide of the invention], immunogenicity (ability to generate antibody which binds to a polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of polypeptides of the invention, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the invention for binding to an antibody of the polypeptide of the invention, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand for a polypeptide of the invention identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel

chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates of binding of a polypeptide of the invention to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the invention and fragments, variants derivatives and analogs thereof to elicit related biological activity related to that of the polypeptide of the invention (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Epitopes and Antibodies

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. Z or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:X or contained in ATCC deposit No. Z under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies

described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to

an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof,

resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins as those described above may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG

Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior

to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any

animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding

epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6}M, 5×10^{-7} M, 10^{7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, $^{10\text{-}12}$ M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferrably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For

example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including

both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not

limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably,

the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g.,

Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human

immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences,

e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used.

As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a

nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein

promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993);

Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991);

Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags

useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-

dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld

et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to

prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the

antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or

prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue- specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or

indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can

be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be

carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of

the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above;

additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein

and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term

"pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry

lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art

(e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging:

The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present

invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled

monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface- bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target

cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).) Polynucleotides comprising or alternatively consisting of nucleic acids which encode these fusion proteins are also encompassed by the invention.

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a

fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the

vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ,pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express the polypeptide of the present invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A

main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. *See*, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a protein of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an

expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination, resulting in the formation of a new transcription unit (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; U.S. Patent No. 5,733,761, issued March 31, 1998; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide sequence of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino

acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses polypeptides which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent NO: 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used,

depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992); Francis *et al., Intern. J. of Hematol. 68*:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992).

The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention

relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, *Therapeutics*) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these polypeptides as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (*e.g.*, containing polypeptides having identical or different amino acid sequences) or a homotrimer (*e.g.*, containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (*i.e.*, polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed

when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in the sequence listing, or contained in the polypeptide encoded by a deposited clone). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein of the invention.

In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in an Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al.,

Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide seuqence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely

modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hyrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers,

since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety)..

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g., Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London

(1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression

level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the present invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the present invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the present invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotide of the present invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the present invention or the level of the mRNA encoding the polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains the polypeptide of the present invention or mRNA. As indicated, biological samples

include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and other tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferrably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the present invention attached may be used to identify polymorphisms between the polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, including cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L.Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide

backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention is useful for detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative diseases, disorders, and/or conditions are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative diseases, disorders, and/or conditions of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression,CRCPress, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information

disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat or prevent disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant,urine,fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR

Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and

technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for

detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat, prevent, and/or diagnose disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat, prevent, and/or diagnose disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treatingor preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the invention that operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the invention *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Belldegrun et al., J. Natl. Cancer Inst., 85:207-216 (1993); Ferrantini et al., Cancer Research, 53:107-1112 (1993); Ferrantini et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato, et al., Human Gene Therapy 7:1-10 (1996); Santodonato, et al., Gene Therapy 4:1246-1255 (1997); and Zhang, et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations,

lipofectin or precipitating agents and the like. However, the polynucleotides of the invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs of the invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of polynucleotide sequence of the invention. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotides of the invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular,

fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked*nucleic* acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs of the invention are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA , 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem., 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication NO: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc. Natl. Acad. Sci. USA, 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP

starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology , 101:512-527 (1983), which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta,

394:483 (1975); Wilson et al., Cell , 17:77 (1979)); ether injection (Deamer et al., Biochim. Biophys. Acta, 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun., 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA, 76:3348 (1979)); detergent dialysis (Enoch et al., Proc. Natl. Acad. Sci. USA , 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem., 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA , 75:145 (1978); Schaefer-Ridder et al., Science, 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent NO: 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding polypeptides of the invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy , 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any

means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding polypeptides of the invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express polypeptides of the invention.

In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotides of the invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses polypeptides of the invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartzet al., Am. Rev. Respir. Dis., 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al.,Science , 252:431-434 (1991); Rosenfeld et al., Cell, 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al. Proc. Natl. Acad. Sci. USA , 76:6606 (1979)).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel., 3:499-503 (1993); Rosenfeld et al., Cell , 68:143-155 (1992); Engelhardt et al., Human Genet. Ther., 4:759-769 (1993); Yang et al., Nature Genet., 7:362-369 (1994); Wilson et al., Nature , 365:691-692 (1993); and U.S. Patent NO: 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and E1b, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other

varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, Curr. Topics in Microbiol. Immunol., 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct containing polynucleotides of the invention is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct of the invention. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the desired gene product.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding the polypeptide sequence of interest) via homologous recombination (see, e.g., U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5′ end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5′ and 3′ ends. Preferably, the 3′ end of the first targeting sequence contains the same restriction enzyme site as the 5′ end of the amplified promoter and the 5′ end of the second targeting sequence contains the same restriction site as the 3′ end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotides encoding polypeptides of the present invention may be administered along with other polynucleotides encoding other angiongenic proteins. Angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

Preferably, the polynucleotide encoding a polypeptide of the invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5′ end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers. (Kaneda et al., Science, 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is

administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA , 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian. Therapeutic compositions of

the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly

Biological Activities

The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

Polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

Immune Activity

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an

immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic

mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of

the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune

complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention

In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose

IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis,

balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositits, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected,

and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune

response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli,* Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi.*

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and

immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment,

compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of

blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or

polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of

the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention in an organ system listed above.

Blood-Related Disorders

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be

important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis

and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hololytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, rhe polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing,

and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction

accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic

regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and

Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute

Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous

Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic

ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including,

but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic

(granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the poynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention

inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for

polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some

of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragements thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragements thereof. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}M$, $10^{-6}M$, $5X10^{-7}M$, $10^{-7}M$, $5X10^{-8}M$, $10^{-8}M$, $5X10^{-9}M$, $10^{-9}M$, $5X10^{-10}M$, $10^{-10}M$, $5X10^{-11}M$, $10^{-11}M$, $5X10^{-12}M$, $10^{-12}M$, $5X10^{-13}M$, $10^{-13}M$, $5X10^{-14}M$, $10^{-14}M$, $5X10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,

Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodes associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide

antibodes of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Renal Disorders

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal

artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the

art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-

branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or

topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal

infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization

including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech. 9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.,* Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and

Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress

(approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and

administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the

compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the polynucleotides, polypeptides, agonists and/or agonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals,

arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl

complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-

316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and

carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to

stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes,

mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy),

systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of

limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al., J. Neurosci., 10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al., Exp. Neurol., 70*:65-82 (1980), or Brown *et al., Ann. Rev. Neurosci., 4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists

or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral

encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as

Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie

Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia,

amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine

system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat, prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, and/or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments the polynucleotides and/or polypeptides

corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

Reproductive System Disorders

The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and

diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a

non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia

gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae,

Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*,

Clostridium perfringens, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea, Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In

specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis,

osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Gastrointestinal Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal

disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver

enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach

rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These

chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express

the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation

factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring

about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation

of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Polypeptides of the Invention Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the

polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:contacting a polypeptide of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptide of the invention.

The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the invention. The molecules having a selective affinity for the polypeptide of the invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of

transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alterntatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptide of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157;

Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine.

Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a polypeptide of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Anitsense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These

experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature, 29:304-310 (1981), the promoter contained in the 3′ long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A., 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., Nature, 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5′ end of the message, *e.g.*, the 5′ untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3′ untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5′ - or 3′ - non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5′ untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5′ -, 3′ - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or

phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556 (1989); Lemaitre et al., Proc. Natl. Acad. Sci., 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., BioTechniques, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, Pharm. Res., 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5′-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited

to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2-0-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5′-UG-3′. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably,

the ribozyme is engineered so that the cleavage recognition site is located near the 5′ end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of

a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

Other Activities

The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A. Also preferred is the above nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A. Further preferred is the above nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A. Similarly preferred is the above nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said isolated nucleic acid molecule does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1A for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA of a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1A. Further preferred is the above nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone. In addition, an isolated nucleic acid molecule of the invention may comprise a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence of the cDNA in said human cDNA clone. A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence of the cDNA in said human cDNA clone. A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of the cDNA in said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least

95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises: (a) a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group; and (b) determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence. The step of comparing sequences in the above method may further comprise determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, the step of comparing sequences in the above method may be performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. This method described above may further comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1A, which method comprises a step of detecting in a

biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. This method described above may further comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A. Further preferred is the above isolated polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. Further preferred is the above isolated polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises: (a) a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group; and (b) determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids. The step in the above method of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group may further comprise determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. Further, the step of comparing sequences in the above method may be performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. This method may further comprise a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1A, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence

of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. Further preferred is the above isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host. Similarly preferred is the above isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecules into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector of the invention into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1A and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1A; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Additional preferred embodiments include the following:

I. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of: (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X; (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity; (f) a polynucleotide which is a variant of SEQ ID NO:X; (g) a polynucleotide which is an allelic variant of SEQ ID NO:X; (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y; and (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

Also preferred is the isolated nucleic acid molecule as described in preferred embodiment I, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein. The nucleotide sequence encoding a secreted protein may further comprise sequential nucleotide deletions from either the C-terminus or the N-terminus.

Also preferred is the isolated nucleic acid molecule as described in preferred embodiment I, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the

cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X. The nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z may further comprise sequential nucleotide deletions from either the C-terminus or the N-terminus.

Also preferred is the isolated nucleic acid molecule as described in preferred embodiment I, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

Also preferred is a recombinant vector comprising the isolated nucleic acid molecule described in preferred embodiment I.

Also preferred is a recombinant host cell comprising the isolated nucleic acid molecule described in preferred embodiment I and the method of making the recombinant host cell. The recombinant host cell may further comprise vector sequences.

Also preferred is a method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising determining the presence or absence of a mutation in the polynucleotide described in preferred embodiment I and diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of the mutation.

II. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of: (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity; (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z; (g) a variant of SEQ ID NO:Y; (h) an allelic variant of SEQ ID NO:Y; and (i) a species homologue of SEQ ID NO:Y.

Also preferred is the isolated polypeptide as described in preferred embodiment II, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

Also preferred is an isolated antibody that binds specifically to the isolated polypeptide described in preferred embodiment II.

Also preferred is a recombinant host cell that expresses the isolated polypeptide described in preferred embodiment II.

Also preferred is a method of making an isolated polypeptide that comprises culturing the recombinant host cells that expresses the isolated polypeptide described in preferred embodiment II and recovering said polypetide. Further envisioned is the polypeptide produced by this method.

Also preferred is a method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising: (a) determining the presence or amount of expression of the polypeptide described in preferred embodiment II in a biological sample; and (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

Also preferred is a method for identifying a binding partner to the polypeptide described in preferred embodiment II comprising: (a) contacting the polypeptide with a binding partner; and (b) determining whether the binding partner effects an activity of the polypeptide

III. The gene corresponding to the cDNA sequence of SEQ ID NO:X.

IV. A method of identifying an activity in a biological assay, wherein the method comprises: (a) expressing SEQ ID NO:X in a cell; (b) isolating the supernatent; (c) detecting an activity in a biological assay; and (d) identifying the protein in the supernatent having the activity. Preferred embodiment IV may further include the product produced by the method.

Also preferred is a method for preventing, treating, or ameliorating a medical condition comprising administering to a mammalian subject a therapeutically effective amount of the polynucleotide described in preferred embodiment I or the polypeptide described in preferred embodiment II.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1A identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1A as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3

primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1A, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1A for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1A. Typically, each ATCC deposit sample cited in Table 1A comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1A. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5′ NT and the 3′ NT of the clone defined in Table 1A) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5′ or 3′ non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5′ and 3′ "RACE" protocols which are well

known in the art. For instance, a method similar to 5′ RACE is available for generating the missing 5′ end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5′ ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5′ portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5′ phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5′ ends of messenger RNAs. This reaction leaves a 5′ phosphate group at the 5′ end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5′ end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5′ end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by,

among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds,95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product

into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D.^{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then

washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a

stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1A, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold™

baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of ^{35}S-methionine and 5 uCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation.

The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J.

L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then

transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 a pC4 is cotransfected with 0.5 ug of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 uM, 2 uM, 5 uM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 uM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by

modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACC
GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCG
TGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCG
CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCAC
GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGA

TGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130

mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_20$; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person

B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

JAKs Ligand		tyk2	Jak1	Jak2	Jak3	STATS	GAS(elements) or ISRE
IFN family							
IFN-a/B	+	+	-	-	1,2,3		ISRE
IFN-g			+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10		+	?	?	-	1,3	
gp130 family							
IL-6 (Pleiotrophic)		+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrophic)		?	+	?	?	1,3	
OnM(Pleiotrophic)		?	+	+	?	1,3	
LIF(Pleiotrophic) ?		+	+	?	1,3		
CNTF(Pleiotrophic)		-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)		?	+	?	?	1,3	
IL-12(Pleiotrophic)		+	-	+	+	1,3	
g-C family							
IL-2 (lymphocytes)		-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)		-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)		-	+	-	+	5	GAS
IL-9 (lymphocytes)		-	+	-	+	5	GAS
IL-13 (lymphocyte)		-	+	?	?	6	GAS
IL-15		?	+	?	+	5	GAS
gp140 family							
IL-3 (myeloid)		-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)		-	-	+	-	5	GAS
GM-CSF (myeloid)		-	-	+	-	5	GAS
Growth hormone family							
GH		?	-	+	-	5	
PRL		?	+/-	+	-	1,3,5	
EPO		?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases							
EGF		?	+	+	-	1,3	GAS (IRF1)
PDGF		?	+	+	-	1,3	
CSF-1		?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152),

although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at –20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by determining whether polypeptides of the invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10e^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing

10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably

transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-

KB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCC GGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC TTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTC CGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATG GCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTG AGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGC AAAAAGCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,

the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5

21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small

molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4 , 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen

Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the

components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against

Erk-1and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degrees C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring

suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulation

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual

patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

In a preferred embodiment, Neutrokine-alpha and/or Neutrokine-alphaSV compositions of the invention are formulated in a biodegradable, polymeric drug delivery system, for example as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,324,519; 5,340,849; and 5,487,897 and in International Publication Numbers WO01/35929, WO00/24374, and WO00/06117 which are hereby incorporated by reference in their entirety. In specific preferred embodiments the Neutrokine-alpha and/or Neutrokine-alphaSV compositions of the invention are formulated using the ATRIGEL® Biodegradable System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Examples of biodegradable polymers which can be used in the formulation of Neutrokine-alpha and/or Neutrokine-alphaSV compositions, include but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those that have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the

biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility. In specific preferred embodiments, the biodegradable polymers which can be used in the formulation of Neutrokine-alpha and/or Neutrokine-alphaSV compositions are poly(lactide-co-glycolides). Polymer properties such as molecular weight, hydrophobicity, and lactide/glycolide ratio may be modified to obtain the desired drug Neutrokine-alpha and/or Neutrokine-alphaSV release profile (See, e.g., Ravivarapu et al., Journal of Pharmaceutical Sciences 89:732-741 (2000), which is hereby incorporated by refernce in its entirety).

It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Examples of such solvents include, but are not limted to, N-methyl-2-pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, C1 to C15 alchohols, dils, triols, and tetraols such as ethanol, glycerine propylene glycol, butanol; C3 to C15 alkyl ketones such as acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; alkyl ketones such as methyl ethyl ketone, C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate, decylmethylsulfoxide, dimethyl sulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one, Other preferred solvents are benzyl alchohol, benzyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. The most preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate because of the solvating ability and their compatibility.

Additionally, formulations comprising Neutrokine-alpha and/or Neutrokine-alphaSV compositions and a biodegradable polymer may also include release-rate modification agents and/or pore-forming agents. Examples of release-rate modification agents include, but are not limited to, fatty acids, triglycerides, other like hydrophobic compounds, organic solvents, plasticizing compounds and hydrophilic compounds. Suitable release rate modification agents include, for example, esters of

mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C.sub.6 -C.sub.12 alkanols, 2-ethoxyethanol, and the like. The release rate modification agent may be used singly or in combination with other such agents. Suitable combinations of release rate modification agents include, but are not limited to, glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred release rate modification agents include, but are not limited to, dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol. Suitable pore-forming agents that may be used in the polymer composition include, but are not limited to, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. Solid crystals that will provide a defined pore size, such as salt or sugar, are preferred.

In specific preferred embodiments the Neutrokine-alpha and/or Neutrokine-alphaSV compositions of the invention are formulated using the BEMA™ BioErodible Mucoadhesive System, MCA™ MucoCutaneous Absorption System, SMP™ Solvent MicroParticle System, or BCP™ BioCompatible Polymer System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); E P 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos.

4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or

arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable prepartions of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in

combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase

inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N

mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al., PNAS 94*:11567-72 (1997); Chen *et al., Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the

anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or

prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the

Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid

derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum

(VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101;

Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not lmited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not lmited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and

Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with

anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma

(International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^+-K^+-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide,

hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™,

ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone

acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and

KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (piogliatazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole,

pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 24: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the

polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA,* 86:8932-8935 (1989); and Zijlstra et al., *Nature,* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2 HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The

resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately $1.5.X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 28: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al.,

Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It

is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over

one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 29: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the

polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 30: Knock-Out Animals.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-

512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The

engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 31: Production of an Antibody

Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler

et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing

chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Isolation Of Antibody Fragments Directed polypeptide(s) of the invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in

300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Purified polypeptides of the invention, or truncated forms thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be

readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10^{-5}M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 33: T Cell Proliferation Assay

Proliferation assay for Resting PBLs.

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washe three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^{4}/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20 C for measurement of IL-2 (or other cytokines) if effect o proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.5 microcuries of ^{3}H-thymidine and cultured at 37 C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of ^{3}H-thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x10^{4} cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control

supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (*), IFN , TNF , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ^{3}H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(*) The amount of the control cytokines IL-2, IFN , TNF and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

Costimulation assay.

A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to

attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 $x10^4$ cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ^{3}H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

Costimulation assay: IFN γ and IL-2 ELISA.

The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using 1 x 10^5 cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the

following proteins: vector only(negative control), IL-2, IFN , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate. Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the assay. ELISAs to test for IFN and IL-2 secretion are performed using kits purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

Proliferation assay for preactivated-resting T cells.

A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then cultured in the presence of low doses of IL-2 resemble effector T cells. These cells are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable to detect the effect of very low doses of an unknown growth factor, that would not be sufficient to induce proliferation on resting (naïve) T cells.

The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the presence of 2ug/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then washed in PBS and cultured in10% FCS/RPMI in the presence of 5ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1%FCS/RPMI) for16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to determine the percentage of T cells (CD3 positive cells) present; this usually ranges between 93-97% depending on the donor. The assay is performed in a 96 well plate

using 2 x10^4 cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of in10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2, IFN , TNF , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ^{3}H-thymidine(Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies

for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6/ml) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e..g, R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be

applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2 x 10^6/ml in PBS containing PI at a final concentration of 5 μg/ml, and then incubaed at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of $5x10^5$ cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e..g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at 2-1x10^5 cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 35: Biological Effects of Polypeptides of the Invention

Astrocyte and Neuronal Assays

Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl.*

Acad. Sci. USA 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays:

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE_2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for PGE_2 by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth

of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of a polypeptide of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm^2 on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for

dopminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, $VEGF_{165}$ or a polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al.* *In Vitro Cell. Dev. Biol. 30A:*512-518 (1994).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of

the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida et al., J. Biol. Chem. 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 39: Stimulation of Endothelial Migration

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8 um (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25 ul of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber, 2.5 x 10^5 cells suspended in 50 ul M199 containing 1% FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO2 to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to

test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:

$$2\ KNO_2 + 2\ KI + 2\ H_2SO_4\ 6\ 2\ NO + I_2 + 2\ H_2O + 2\ K_2SO_4$$

The standard calibration curve is obtained by adding graded concentrations of KNO_2 (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing KI and H_2SO_4. The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C. The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions. S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per $1x10^6$ endothelial cells. All values reported are

means of four to six measurements in each group (number of cell culture wells). See, Leak *et al. Biochem. and Biophys. Res. Comm. 217*:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 41: Effect of Polypepides of the Invention on Cord Formation in Angiogenesis

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 ml/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 mg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese qual (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of 16-day-old chick and 13-day-old qual embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cellotape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse

In vivo angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 44: Rescue of Ischemia in Rabbit Lower Limb Model

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol 147*:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita*et al. Am J. Pathol 147*:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al. Hum Gene Ther. 4*:749-758

(1993); Leclerc *et al. J. Clin. Invest. 90*: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1 min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number m the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

Example 45: Effect of Polypeptides of the Invention on Vasodilation

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean +/- SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as $p<0.05$ vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 46: Rat Ischemic Skin Flap Model

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

Ischemic skin

Ischemic skin wounds

Normal wounds

The experimental protocol includes:

Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).

An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).

Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.

Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 47: Peripheral Arterial Disease Model

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.

The ischemic muscle tissue is collected after ligation of the femoral artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 48: Ischemic Myocardial Disease Model

A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 49: Rat Corneal Wound Healing Model

This animal model shows the effect of a polypeptide of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer. Inserting a spatula below the lip of the incision facing the outer corner of the eye. Making

a pocket (its base is 1-1.5 mm form the edge of the eye). Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

Diabetic db+/db+ Mouse Model.

To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al., J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al., Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al., Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al., Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al., Diabetes 29(1)*:60-67 (1980); Giacomelli *et al.,*

Lab Invest. 40(4):460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al., J. Immunol. 120*:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al., Am. J. of Pathol. 136*:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm^2, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136:*1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a negative tissue control. Each specimen includes a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al., An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al., Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

To demonstrate that a polypeptide of the invention can accelerate the healing process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 51: Lymphadema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of a polypeptide of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and

histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing

perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca2+ comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 52: Suppression of TNF alpha-induced adhesion molecule expression by a Polypeptide of the Invention

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules

(CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO_2. HUVECs are seeded in 96-well plates at concentrations of 1 x 10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are

aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 µl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x 10^5 cells/ml. During this time, 100 µl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 µl of prepared cytokines, 50 µl SID (supernatants at 1:2 dilution = 50 µl) and 20 µl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 µl. The plates are then placed in a 37°C/5% CO_2 incubator for five days.

Eighteen hours before the assay is harvested, 0.5 µCi/well of [3H] Thymidine is added in a 10 µl volume to each well to determine the proliferation rate. The

experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 µl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM.

Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 $\mu g/ cm^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2, 7% O_2, and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular gene product is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 µl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin,

2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μg/ml hEGF, 5mg/ml insulin, 1μg/ml hFGF, 50mg/ml gentamycin, 50 μg/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50μg/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO_2 until day 5.

Transfer 60μl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100 μl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10μl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the

gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 µl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 µl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 µl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are

incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution, refered to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 57: Alamar Blue Endothelial Cells Proliferation Assay

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with

GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes,

inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 µl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 µg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 µC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other

disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Additionally, the specificatons and sequence listings of U.S. Patent Application Serial No. 09/482,273, filed January 13, 2000; International Patent Application Serial Nos: PCT/US99/15849 and PCT/US01/00911, filed July 14, 1999 and January 12, 2001, respectively; U.S. Provisional Patent Application Serial No. 60/234,925, filed September 25, 2000; and U.S. Provisional Patent Applications Serial Nos. 60/092,921, 60/092,922, and 60/092,956, filed July 15, 1998 are hereby incorporated by reference in their entirety.

Table 6

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	A	.	.	.	.	.	-0.77	0.40	*	*	.	-0.60	0.38
Ala	2	A	A	.	.	.	.	.	-0.27	0.40	*	*	.	-0.60	0.30
Ala	3	A	A	.	.	.	.	.	-0.69	-0.03	*	*	.	0.30	0.45
Ala	4	A	A	.	.	.	.	.	-0.51	0.23	*	*	.	-0.30	0.38
Gly	5	A	.	.	.	.	.	.	-0.42	0.04	*	*	.	0.03	0.58
Arg	6	.	.	.	.	.	.	C	-0.12	-0.07	*	*	F	1.11	0.77
Leu	7	.	.	.	.	.	.	C	0.18	-0.19	*	*	F	1.39	1.02
Pro	8	.	.	.	.	.	T	C	0.18	0.23	*	*	F	1.12	1.08
Ser	9	.	.	.	.	T	T	.	-0.04	0.30	*	*	F	1.30	0.56
Ser	10	.	.	B	.	.	T	.	-0.40	0.99	*	*	F	0.47	0.56
Trp	11	.	.	B	.	.	T	.	-0.81	1.09	*	*	.	0.19	0.31
Ala	12	.	.	B	B	.	.	.	-0.21	1.04	.	.	.	-0.34	0.31
Leu	13	.	.	B	B	.	.	.	-0.81	1.09	.	.	.	-0.47	0.36
Phe	14	.	.	B	B	.	.	.	-1.32	1.39	.	.	.	-0.60	0.28
Ser	15	.	.	B	.	.	T	.	-1.61	1.16	.	.	.	-0.20	0.23
Pro	16	.	.	B	.	.	T	.	-1.67	1.16	*	.	.	-0.20	0.28
Leu	17	A	.	.	.	.	T	.	-1.89	0.90	.	.	.	-0.20	0.32
Leu	18	A	.	.	.	.	T	.	-1.67	0.80	.	.	.	-0.20	0.20
Ala	19	A	A	.	.	.	.	.	-1.78	0.91	.	.	.	-0.60	0.13
Gly	20	A	A	.	.	.	.	.	-2.29	1.17	.	.	.	-0.60	0.13
Leu	21	A	A	.	.	.	.	.	-2.42	1.17	.	.	.	-0.60	0.13
Ala	22	.	A	B	.	.	.	.	-2.47	0.91	.	.	.	-0.60	0.13
Leu	23	.	A	B	.	.	.	.	-2.00	1.06	.	.	.	-0.60	0.10
Leu	24	.	A	B	.	.	.	.	-1.62	1.06	.	.	.	-0.60	0.11
Gly	25	.	A	B	.	.	.	.	-2.13	0.80	.	.	.	-0.60	0.18
Val	26	.	.	B	.	.	.	.	-1.53	0.94	.	.	.	-0.40	0.16
Gly	27	.	.	B	.	.	.	.	-1.53	0.69	*	*	F	-0.25	0.30
Pro	28	.	.	B	.	.	.	.	-0.61	0.50	*	*	F	-0.25	0.30
Val	29	.	.	B	.	.	.	.	-0.39	0.07	*	*	F	0.05	0.80
Pro	30	.	A	B	.	.	.	.	-0.86	-0.07	*	*	.	0.30	0.81
Ala	31	A	A	B	.	.	.	.	-0.03	0.19	*	*	.	-0.30	0.43
Arg	32	A	A	.	.	.	.	.	0.31	0.26	*	*	.	-0.30	0.80
Ala	33	A	A	.	.	.	.	.	-0.33	0.01	*	*	.	-0.30	0.83
Leu	34	A	A	.	.	.	.	.	0.21	0.23	*	*	.	-0.30	0.61
His	35	A	A	.	.	.	.	.	-0.17	0.21	*	*	.	-0.30	0.45
Asn	36	A	A	B	.	.	.	.	0.42	0.71	*	*	.	-0.60	0.45
Val	37	A	A	.	.	.	.	.	-0.50	0.21	*	*	.	-0.30	0.94
Thr	38	A	A	.	.	.	.	.	-0.61	0.21	*	.	.	-0.30	0.57
Ala	39	A	A	.	.	.	.	.	-0.14	0.50	*	.	.	-0.60	0.31
Glu	40	A	A	.	.	.	.	.	-0.70	0.53	.	*	.	-0.60	0.41
Leu	41	A	A	.	.	.	.	.	-0.70	0.39	.	*	.	-0.30	0.29
Phe	42	A	A	.	.	.	.	.	-0.43	-0.10	.	.	.	0.30	0.49
Gly	43	A	A	.	.	.	.	.	-0.41	-0.10	.	.	.	0.30	0.29
Ala	44	A	A	.	.	.	.	.	-0.17	0.81	.	.	.	-0.60	0.37
Glu	45	A	A	.	.	.	.	.	-0.48	0.56	.	.	.	-0.60	0.42
Ala	46	A	A	.	.	.	.	.	-0.48	0.26	.	.	.	-0.30	0.61
Trp	47	A	A	.	.	.	.	.	-0.37	0.51	.	*	.	-0.60	0.50
Gly	48	A	A	.	.	.	.	.	-0.61	0.51	.	.	.	-0.60	0.29
Thr	49	A	A	.	.	.	.	.	-0.72	1.01	.	.	.	-0.60	0.29
Leu	50	A	A	.	.	.	.	.	-1.07	1.30	*	.	.	-0.60	0.24
Ala	51	A	A	.	.	.	.	.	-0.48	0.81	.	.	.	-0.60	0.24
Ala	52	A	A	.	.	.	.	.	-1.00	0.39	.	*	.	-0.30	0.28
Phe	53	A	A	.	.	.	.	.	-0.66	0.59	.	*	.	-0.60	0.28
Gly	54	A	.	.	.	.	.	.	-0.64	0.30	.	*	.	-0.10	0.44
Asp	55	A	.	.	.	.	.	.	0.17	0.19	.	.	F	0.39	0.58
Leu	56	.	.	.	.	.	.	C	0.80	-0.31	.	.	F	1.68	1.12
Asn	57	.	.	.	.	.	T	C	1.39	-1.10	.	.	F	2.52	2.27
Ser	58	.	.	.	.	.	T	C	1.78	-1.13	.	*	F	2.86	2.36
Asp	59	.	.	.	.	T	T	.	2.12	-0.64	.	*	F	3.40	4.12

	Lys	60	A	.	.	.	.	T	.	1.31	-1.33	.	*	F	2.66	4.28
	Gln	61	A	.	.	B	.	.	.	1.42	-1.04	.	*	F	1.92	2.64
	Thr	62	A	.	.	B	.	.	.	0.57	-0.64	.	.	F	1.58	1.37
	Asp	63	.	.	B	B	.	.	.	0.06	0.00	.	.	F	0.19	0.51
5	Leu	64	.	.	B	B	.	.	.	0.17	0.69	.	.	.	-0.60	0.24
	Phe	65	.	.	B	B	.	.	.	0.12	0.29	.	*	.	-0.30	0.33
	Val	66	.	.	B	B	.	.	.	0.23	-0.20	.	*	.	0.30	0.34
	Leu	67	A	.	.	B	.	.	.	0.54	-0.20	.	*	.	0.30	0.81
	Arg	68	A	.	.	B	.	.	.	0.54	-0.49	.	*	F	0.60	1.50
10	Glu	69	A	.	.	.	.	T	.	0.54	-1.27	.	*	F	1.30	3.37
	Arg	70	A	.	.	.	.	T	.	0.36	-1.23	.	*	F	1.30	3.37
	Asn	71	A	.	.	.	.	T	.	0.36	-1.23	*	*	F	1.30	1.21
	Asp	72	A	.	.	.	.	T	.	0.47	-0.59	*	*	F	1.15	0.52
	Leu	73	A	.	.	B	.	.	.	-0.46	0.20	.	*	.	-0.30	0.23
15	Ile	74	.	.	B	B	.	.	.	-1.04	0.89	.	.	.	-0.60	0.12
	Val	75	.	.	B	B	.	.	.	-1.16	0.99	.	.	.	-0.60	0.07
	Phe	76	.	.	B	B	.	.	.	-1.16	0.99	.	.	.	-0.60	0.14
	Leu	77	.	.	B	B	.	.	.	-1.16	0.70	.	.	.	-0.36	0.35
	Ala	78	A	.	.	B	.	.	.	-0.93	0.41	.	.	.	-0.12	0.77
20	Asp	79	A	.	.	.	.	T	.	-0.26	0.27	.	.	F	0.97	0.90
	Gln	80	.	.	.	.	T	T	.	0.36	-0.09	.	.	F	2.36	1.68
	Asn	81	.	.	.	.	.	T	C	0.36	-0.01	.	.	F	2.40	2.61
	Ala	82	.	.	.	.	.	T	C	1.21	0.27	*	.	F	1.56	1.35
	Pro	83	A	.	.	.	.	.	.	1.59	0.27	.	*	.	0.77	1.56
25	Tyr	84	.	.	.	.	T	.	.	1.63	0.30	.	*	.	0.93	1.50
	Phe	85	.	.	B	.	.	.	.	0.78	-0.10	*	*	.	0.89	2.97
	Lys	86	.	.	B	.	.	.	.	0.82	0.04	.	*	F	0.20	1.43
	Pro	87	.	.	B	.	.	.	.	0.56	-0.39	.	*	F	0.80	1.82
	Lys	88	A	.	.	B	.	.	.	0.47	-0.50	.	*	F	0.60	1.56
30	Val	89	A	.	.	B	.	.	.	0.01	-0.90	*	*	F	0.90	1.05
	Lys	90	A	.	.	B	.	.	.	0.76	-0.11	*	*	F	0.45	0.59
	Val	91	A	.	.	B	.	.	.	0.71	-0.54	.	*	.	0.60	0.59
	Ser	92	A	.	.	.	.	.	.	0.89	-0.14	.	*	.	0.65	1.27
	Phe	93	A	.	.	.	.	.	.	0.54	-0.29	.	*	.	0.50	0.86
35	Lys	94	A	.	.	.	.	.	.	0.81	0.10	*	*	.	0.05	1.56
	Asn	95	A	.	.	.	.	.	.	-0.04	-0.04	*	*	.	0.65	1.18
	His	96	A	.	.	.	.	.	.	-0.08	0.26	.	*	.	0.05	1.12
	Ser	97	A	.	.	B	.	.	.	-0.09	0.16	*	.	.	-0.30	0.39
	Ala	98	.	.	B	B	.	.	.	0.31	0.64	*	.	.	-0.60	0.35
40	Leu	99	.	.	B	B	.	.	.	-0.59	0.63	*	.	.	-0.60	0.35
	Ile	100	.	.	B	B	.	.	.	-1.44	0.77	.	.	.	-0.60	0.19
	Thr	101	.	.	B	B	.	.	.	-1.62	1.03	.	.	.	-0.60	0.14
	Ser	102	.	.	B	B	.	.	.	-1.67	0.96	.	.	.	-0.60	0.26
	Val	103	.	.	B	B	.	.	.	-1.08	0.70	.	.	.	-0.60	0.37
45	Val	104	.	.	B	.	.	T	.	-0.51	0.01	*	.	F	0.25	0.43
	Pro	105	.	.	B	.	.	T	.	0.38	0.29	*	*	F	0.59	0.51
	Gly	106	.	.	.	.	T	T	.	0.34	-0.10	.	*	F	2.08	1.14
	Asp	107	.	.	.	.	T	T	.	0.64	-0.31	.	*	F	2.42	1.52
	Tyr	108	.	.	.	.	T	.	.	1.20	-0.96	.	*	F	2.86	1.64
50	Asp	109	.	.	.	.	T	T	.	2.06	-1.00	.	*	F	3.40	2.22
	Gly	110	.	.	.	.	T	T	.	1.67	-1.03	.	*	F	3.06	2.30
	Asp	111	.	.	.	.	T	T	.	2.01	-0.41	.	*	F	2.42	1.45
	Ser	112	.	.	B	.	.	T	.	1.16	-1.17	.	*	F	1.98	1.45
	Gln	113	.	.	B	B	.	.	.	0.59	-0.53	.	*	F	1.24	1.09
55	Met	114	.	.	B	B	.	.	.	-0.22	-0.27	.	*	.	0.30	0.54
	Asp	115	.	.	B	B	.	.	.	-0.19	0.41	.	*	.	-0.60	0.33
	Val	116	.	.	B	B	.	.	.	-0.43	0.51	*	*	.	-0.60	0.28
	Leu	117	.	.	B	B	.	.	.	-0.94	0.87	*	*	.	-0.60	0.44
	Leu	118	.	.	B	B	.	.	.	-1.16	0.94	*	*	.	-0.60	0.22
60	Thr	119	.	.	B	B	.	.	.	-0.51	1.37	*	.	.	-0.60	0.45
	Tyr	120	.	.	B	.	.	.	.	-0.51	0.73	*	.	.	-0.25	1.09
	Leu	121	.	.	B	.	.	.	.	0.10	0.44	*	.	.	-0.25	2.13
	Pro	122	A	.	.	.	.	T	.	0.32	0.51	*	.	F	0.10	2.31

	Lys	123	.	.	.	.	T	T	.	1.18	0.53	*	.	F	0.50	1.49
	Asn	124	.	.	.	.	.	T	C	1.19	-0.23	*	.	F	1.20	3.61
	Tyr	125	A	.	.	.	.	T	.	1.43	-0.53	.	*	F	1.30	3.13
	Ala	126	A	A	.	.	.	.	.	1.43	-0.96	.	*	F	0.90	2.71
5	Lys	127	A	A	.	.	.	.	.	1.30	-0.27	.	*	F	0.60	1.39
	Ser	128	A	A	.	.	.	.	.	0.67	-0.24	*	*	F	0.45	0.88
	Glu	129	A	A	.	.	.	.	.	-0.19	-0.50	*	*	F	0.75	0.88
	Leu	130	A	.	.	B	.	.	.	-0.83	-0.36	.	*	.	0.30	0.33
	Gly	131	.	.	B	B	.	.	.	-0.94	0.33	.	*	.	-0.30	0.17
10	Ala	132	.	.	B	B	.	.	.	-1.28	0.73	.	*	.	-0.60	0.09
	Val	133	.	.	B	B	.	.	.	-1.32	1.64	.	.	.	-0.60	0.11
	Ile	134	.	.	B	B	.	.	.	-1.32	1.39	.	.	.	-0.60	0.11
	Phe	135	.	.	B	B	.	.	.	-0.51	1.36	.	.	.	-0.60	0.19
	Trp	136	.	.	B	B	.	.	.	-0.17	1.26	.	.	.	-0.60	0.40
15	Gly	137	.	.	.	.	.	T	C	0.11	1.01	.	.	F	0.15	1.00
	Gln	138	.	.	.	.	T	T	.	0.16	0.81	.	.	F	0.50	1.66
	Asn	139	.	.	.	.	.	T	C	1.04	0.71	.	.	F	0.54	1.30
	Gln	140	.	.	.	.	.	T	C	1.53	-0.20	.	.	F	1.68	2.20
	Thr	141	.	.	.	.	.	.	C	1.82	-0.20	.	.	F	1.72	1.96
20	Leu	142	.	.	.	.	.	.	C	2.17	-0.20	.	.	F	1.96	1.96
	Asp	143	.	.	.	.	.	T	C	1.57	-0.20	.	.	F	2.40	1.82
	Pro	144	.	.	.	.	.	T	C	1.26	0.01	.	.	F	1.56	1.25
	Asn	145	.	.	.	.	T	T	.	0.37	0.01	.	.	F	1.52	2.19
	Asn	146	.	.	B	.	.	T	.	-0.13	0.01	.	.	F	0.73	0.92
25	Met	147	.	.	B	B	.	.	.	0.68	0.70	*	*	.	-0.36	0.49
	Thr	148	.	.	B	B	.	.	.	0.79	0.67	*	.	.	-0.60	0.49
	Ile	149	.	.	B	B	.	.	.	0.69	0.27	*	.	.	-0.30	0.60
	Leu	150	.	.	B	B	.	.	.	-0.01	0.36	*	.	.	-0.30	0.87
	Asn	151	.	.	B	B	.	.	.	-0.01	0.53	*	.	.	-0.38	0.52
30	Arg	152	.	.	B	B	.	.	.	0.59	0.44	*	.	F	0.14	1.29
	Thr	153	.	.	.	B	.	.	C	0.90	-0.24	*	.	F	1.46	2.61
	Phe	154	.	.	.	B	.	.	C	1.58	-0.93	*	.	F	1.98	2.81
	Gln	155	.	.	.	B	.	.	C	1.58	-0.90	*	.	F	2.20	2.22
	Asp	156	.	.	.	B	.	.	C	0.69	-0.21	*	.	F	1.68	1.27
35	Glu	157	.	.	B	.	.	.	.	-0.02	-0.01	*	.	F	1.46	1.03
	Pro	158	.	.	B	.	.	.	.	0.29	-0.19	.	.	F	1.09	0.59
	Leu	159	.	.	B	.	.	.	.	0.29	-0.59	.	*	.	1.02	0.59
	Ile	160	A	.	.	.	.	.	.	0.29	0.20	.	*	.	-0.10	0.29
	Met	161	A	.	.	.	.	.	.	-0.06	0.60	.	*	.	-0.15	0.30
40	Asp	162	A	.	.	.	.	T	.	-0.06	0.60	*	*	.	0.30	0.37
	Phe	163	.	.	B	.	.	T	.	-0.66	-0.09	*	*	.	1.45	0.87
	Asn	164	.	.	.	.	T	T	.	-0.73	-0.09	*	*	F	2.25	0.73
	Gly	165	.	.	.	.	T	T	.	-0.06	-0.01	*	*	F	2.50	0.30
	Asp	166	.	.	.	B	T	.	.	0.54	0.41	*	*	F	0.95	0.54
45	Leu	167	.	.	.	B	.	.	C	-0.34	-0.37	*	*	F	1.40	0.57
	Ile	168	.	.	B	B	.	.	.	-0.34	-0.09	*	*	F	0.95	0.40
	Pro	169	.	.	B	B	.	.	.	-0.69	0.27	*	*	.	-0.05	0.21
	Asp	170	.	.	B	B	.	.	.	-1.23	0.70	*	.	.	-0.60	0.25
	Ile	171	.	.	B	B	.	.	.	-1.54	0.70	*	.	.	-0.60	0.25
50	Phe	172	.	.	B	B	.	.	.	-0.73	0.50	*	.	.	-0.60	0.23
	Gly	173	.	.	B	B	.	.	.	0.16	0.47	*	.	.	-0.60	0.22
	Ile	174	.	.	B	B	.	.	.	0.07	0.47	.	.	.	-0.60	0.55
	Thr	175	.	.	.	B	.	.	C	0.07	0.17	*	.	F	0.35	0.86
	Asn	176	.	.	.	B	.	.	C	0.96	-0.21	*	.	F	1.40	1.39
55	Glu	177	.	.	.	.	T	T	.	1.44	-0.24	.	.	F	2.30	3.44
	Ser	178	.	.	.	.	T	T	.	1.79	-0.50	.	.	F	2.60	3.68
	Asn	179	.	.	.	.	.	T	C	1.79	-0.59	.	.	F	3.00	3.97
	Gln	180	.	.	.	.	.	T	C	1.29	-0.30	.	.	F	2.40	1.61
	Pro	181	.	.	B	B	.	.	.	0.48	0.39	.	.	F	0.75	0.99
60	Gln	182	.	.	B	B	.	.	.	0.13	0.69	.	.	F	0.15	0.51
	Ile	183	.	.	B	B	.	.	.	0.09	0.71	.	*	.	-0.30	0.29
	Leu	184	.	.	B	B	.	.	.	0.09	0.74	.	*	.	-0.60	0.19
	Leu	185	.	.	B	B	.	.	.	-0.72	0.71	.	*	.	-0.60	0.17

	Gly	186	.	.	.	.	T	T	.	-0.81	1.00	.	*	F	0.35	0.20
	Gly	187	.	.	.	.	T	T	.	-1.10	0.70	.	*	F	0.35	0.33
	Asn	188	.	.	.	.	.	T	C	-0.24	0.93	.	*	F	0.15	0.42
	Leu	189	.	.	.	.	.	T	C	0.36	0.74	.	*	.	0.00	0.58
5	Ser	190	.	.	.	.	T	.	.	0.58	0.74	.	*	.	0.00	0.90
	Trp	191	.	.	B	.	.	.	.	0.11	0.81	.	*	.	-0.40	0.57
	His	192	.	.	B	.	.	.	.	0.14	1.10	.	*	.	-0.40	0.57
	Pro	193	.	.	B	.	.	.	.	-0.17	0.90	.	*	.	-0.40	0.61
	Ala	194	.	.	B	B	.	.	.	0.33	1.00	.	*	.	-0.60	0.84
10	Leu	195	A	.	.	B	.	.	.	0.33	0.57	*	.	.	-0.60	0.89
	Thr	196	A	.	.	B	.	.	.	0.67	0.46	*	*	F	-0.25	0.77
	Thr	197	A	.	.	.	.	T	C	0.10	0.03	.	*	F	1.00	1.52
	Thr	198	A	.	.	.	.	T	.	0.42	0.14	.	*	F	1.00	1.83
	Ser	199	A	.	.	.	.	T	.	0.12	-0.54	.	*	F	2.10	2.48
15	Lys	200	.	.	B	.	.	T	.	0.72	-0.34	.	*	F	2.00	1.20
	Met	201	.	.	B	.	.	.	.	1.00	-0.40	.	*	F	1.60	1.29
	Arg	202	.	.	B	.	.	.	.	1.01	-0.39	.	*	.	1.25	1.31
	Ile	203	.	.	B	.	.	T	.	1.29	-0.39	.	*	.	1.10	0.88
	Pro	204	.	.	B	.	.	T	.	1.00	0.11	.	*	.	0.45	1.21
20	His	205	A	.	.	.	.	T	.	0.26	0.00	.	*	.	0.10	0.62
	Ser	206	.	.	.	.	.	T	C	-0.03	0.79	.	*	.	0.00	0.77
	His	207	A	A	.	.	.	.	.	-0.14	0.79	.	*	.	-0.60	0.35
	Ala	208	.	A	B	.	.	.	.	-0.07	0.36	.	*	.	-0.30	0.43
	Phe	209	.	A	B	.	.	.	.	-0.17	0.54	*	.	.	-0.60	0.26
25	Ile	210	.	A	B	.	.	.	.	-0.13	0.64	*	*	.	-0.60	0.28
	Asp	211	A	A	.	.	.	.	.	0.17	0.14	*	*	.	-0.30	0.48
	Leu	212	A	A	.	.	.	.	.	-0.50	-0.36	*	*	.	0.30	0.92
	Thr	213	A	A	.	.	.	.	.	-0.22	-0.36	*	*	F	0.60	1.14
	Glu	214	A	A	.	.	.	.	.	-0.11	-0.56	*	*	F	0.75	0.99
30	Asp	215	A	A	.	.	.	.	.	0.78	-0.06	*	*	F	0.60	1.21
	Phe	216	A	A	.	.	.	.	.	-0.03	-0.74	*	*	F	0.90	1.40
	Thr	217	A	A	.	.	.	.	.	0.08	-0.54	.	*	.	0.60	0.67
	Ala	218	A	A	.	.	.	.	.	-0.42	0.24	.	*	.	-0.30	0.35
	Asp	219	A	.	.	B	.	.	.	-0.73	0.93	.	*	.	-0.60	0.33
35	Leu	220	A	.	.	B	.	.	.	-1.04	0.63	.	*	.	-0.60	0.33
	Phe	221	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.60	0.47
	Leu	222	A	.	.	B	.	.	.	-0.84	0.81	*	.	.	-0.60	0.23
	Thr	223	A	.	.	B	.	.	.	-0.84	1.21	*	.	.	-0.60	0.45
	Thr	224	.	.	B	B	.	.	.	-1.16	1.03	*	.	.	-0.60	0.53
40	Leu	225	.	.	.	B	.	.	C	-0.66	0.73	.	.	F	-0.25	0.92
	Asn	226	.	.	.	B	.	.	C	-0.26	0.53	.	.	F	-0.25	0.92
	Ala	227	.	.	.	B	.	.	C	0.24	0.43	.	.	F	-0.25	0.86
	Thr	228	.	.	.	B	.	.	C	-0.14	0.43	*	.	F	-0.10	1.50
	Thr	229	.	.	.	B	.	.	C	0.17	0.53	.	*	F	-0.25	0.81
45	Ser	230	.	.	.	B	.	.	C	0.28	0.53	.	*	F	-0.10	1.38
	Thr	231	.	.	B	B	.	.	.	0.28	0.81	.	*	F	-0.45	0.83
	Phe	232	.	.	B	B	.	.	.	-0.02	0.33	.	*	.	-0.30	1.00
	Gln	233	.	.	B	B	.	.	.	0.00	0.53	.	*	.	-0.60	0.52
	Phe	234	.	.	B	B	.	.	.	0.31	1.06	.	*	.	-0.60	0.38
50	Glu	235	.	.	B	B	.	.	.	0.61	0.57	*	*	.	-0.60	0.76
	Ile	236	A	A	.	.	.	.	.	0.11	0.19	*	*	.	-0.30	0.71
	Trp	237	A	A	.	.	.	.	.	0.81	0.47	.	*	.	-0.60	0.67
	Glu	238	A	A	.	.	.	.	.	0.47	-0.31	.	*	.	0.43	0.65
	Asn	239	.	A	.	.	T	.	.	1.17	0.11	*	*	F	0.51	0.91
55	Leu	240	.	A	.	.	.	.	C	0.47	-0.17	*	*	F	1.19	1.40
	Asp	241	.	.	.	.	T	T	.	1.06	-0.30	*	*	F	1.77	0.70
	Gly	242	.	.	.	.	T	T	.	0.49	0.09	.	*	F	1.30	0.58
	Asn	243	.	.	.	.	.	T	C	0.19	0.33	.	*	F	0.97	0.52
	Phe	244	.	.	.	.	.	T	C	-0.12	0.03	.	*	.	0.69	0.42
60	Ser	245	.	.	B	B	.	.	.	-0.20	0.51	.	*	.	-0.34	0.61
	Val	246	.	.	B	B	.	.	.	-1.01	0.77	*	*	.	-0.47	0.27
	Ser	247	.	.	B	B	.	.	.	-0.67	1.06	*	*	.	-0.60	0.25
	Thr	248	.	.	B	B	.	.	.	-0.62	0.27	*	*	.	-0.30	0.33

	Ile	249	.	.	B	B	.	.	.	-0.13	-0.11	*	.	.	0.30	0.89
	Leu	250	A	.	.	B	.	.	.	0.17	-0.33	*	.	F	0.60	1.02
	Glu	251	A	.	.	B	.	.	.	1.02	-0.31	*	.	F	0.60	1.23
	Lys	252	A	.	.	.	.	.	.	0.72	-0.40	*	.	F	0.80	2.82
5	Pro	253	A	.	.	.	.	T	.	0.43	-0.47	*	.	F	1.00	3.38
	Gln	254	A	.	.	.	.	T	.	0.47	-0.54	*	.	F	1.30	1.93
	Asn	255	A	.	.	.	.	T	.	0.42	0.10	.	.	.	0.10	0.72
	Met	256	.	.	B	.	.	T	.	0.08	0.74	.	.	.	-0.20	0.34
	Met	257	.	.	B	B	.	.	.	0.03	0.74	.	.	.	-0.60	0.20
10	Val	258	.	.	B	B	.	.	.	-0.06	0.74	*	.	.	-0.60	0.21
	Val	259	.	.	B	B	.	.	.	-0.64	0.73	*	.	.	-0.60	0.29
	Gly	260	.	.	B	.	.	.	.	-1.34	0.61	.	.	F	-0.25	0.29
	Gln	261	.	A	B	.	.	.	.	-1.33	0.79	.	.	F	-0.45	0.34
	Ser	262	.	A	B	.	.	.	.	-0.73	0.64	.	.	F	-0.45	0.47
15	Ala	263	.	A	B	.	.	.	.	-0.58	0.00	.	*	.	-0.30	0.79
	Phe	264	.	A	B	.	.	.	.	0.28	0.36	*	*	.	-0.30	0.39
	Ala	265	.	A	B	.	.	.	.	0.28	-0.04	.	*	.	0.61	0.49
	Asp	266	A	A	.	.	.	.	.	0.28	0.00	.	*	.	0.32	0.48
	Phe	267	A	A	.	.	.	.	.	0.23	-0.50	.	*	.	1.23	0.92
20	Asp	268	.	.	.	.	T	T	.	0.79	-0.86	.	*	F	2.79	0.91
	Gly	269	.	.	.	.	T	T	.	0.89	-0.86	.	*	F	3.10	0.74
	Asp	270	A	.	.	.	.	T	.	1.48	-0.24	.	*	F	2.09	0.84
	Gly	271	A	.	.	.	.	T	.	1.44	-1.03	.	*	F	2.08	0.84
	His	272	A	A	.	.	.	.	.	1.33	-0.53	.	*	.	1.37	1.16
25	Met	273	A	A	.	.	.	.	.	0.52	-0.27	*	*	.	0.61	0.57
	Asp	274	.	A	B	.	.	.	.	0.66	0.41	.	*	.	-0.60	0.48
	His	275	.	A	B	.	.	.	.	0.31	0.41	.	.	.	-0.60	0.54
	Leu	276	.	A	B	.	.	.	.	-0.01	0.34	.	.	.	-0.30	0.54
	Leu	277	.	.	B	.	.	T	.	0.02	0.30	*	.	.	0.10	0.17
30	Pro	278	.	.	.	.	T	T	.	0.62	0.30	*	.	F	0.65	0.22
	Gly	279	.	.	.	.	T	T	.	0.67	-0.20	.	.	F	1.25	0.45
	Cys	280	A	.	.	.	.	T	.	0.70	-0.89	.	.	F	1.64	1.09
	Glu	281	A	.	.	.	.	.	.	0.84	-1.17	.	.	F	1.78	1.13
	Asp	282	A	.	.	.	.	T	.	1.66	-1.03	.	.	F	2.17	0.61
35	Lys	283	A	.	.	.	.	T	.	1.91	-1.06	.	.	F	2.66	1.98
	Asn	284	.	.	.	.	T	T	.	1.96	-1.63	.	.	F	3.40	2.29
	Cys	285	A	.	.	.	.	T	.	2.31	-1.24	.	.	F	2.66	1.83
	Gln	286	A	.	.	.	.	T	.	1.42	-0.76	.	.	F	2.32	1.32
	Lys	287	.	.	.	.	T	T	.	1.18	-0.07	*	.	F	1.93	0.58
40	Ser	288	.	.	B	.	.	T	.	0.32	0.29	*	.	F	0.74	1.69
	Thr	289	.	.	B	.	.	T	.	-0.53	0.40	*	.	F	0.25	0.80
	Ile	290	.	.	B	B	.	.	.	0.24	0.64	*	.	.	-0.60	0.30
	Tyr	291	.	.	B	B	.	.	.	-0.06	0.64	*	.	.	-0.60	0.44
	Leu	292	.	.	B	B	.	.	.	-0.44	0.64	*	.	.	-0.26	0.40
45	Val	293	.	.	B	.	.	T	.	-0.74	0.59	*	*	.	0.48	0.57
	Arg	294	.	.	B	.	.	T	.	-0.39	0.51	*	.	F	0.97	0.36
	Ser	295	.	.	.	.	T	T	.	0.50	-0.24	*	.	F	2.61	0.87
	Gly	296	.	.	.	.	T	T	.	0.46	-0.53	*	*	F	3.40	2.04
	Met	297	.	.	.	.	T	.	.	0.41	-0.26	*	*	F	2.56	1.10
50	Lys	298	.	.	.	B	T	.	.	1.06	0.39	*	*	F	1.27	0.61
	Gln	299	.	.	B	B	.	.	.	0.09	0.43	*	*	.	0.08	0.95
	Trp	300	.	.	B	B	.	.	.	-0.42	0.64	*	.	.	-0.26	0.71
	Val	301	.	.	B	B	.	.	.	-0.08	0.71	*	.	.	-0.60	0.29
	Pro	302	.	.	B	B	.	.	.	0.52	1.11	*	.	.	-0.60	0.29
55	Val	303	.	.	B	B	.	.	.	-0.22	0.71	*	.	.	-0.60	0.47
	Leu	304	.	.	B	B	.	.	.	-0.52	0.59	*	.	.	-0.60	0.54
	Gln	305	.	.	B	B	.	.	.	-0.23	0.33	*	.	.	0.04	0.47
	Asp	306	.	.	.	B	T	.	.	0.67	0.30	*	.	F	1.08	1.02
	Phe	307	.	.	.	.	T	.	.	0.53	-0.34	*	.	F	2.22	2.47
60	Ser	308	.	.	.	.	.	.	C	1.08	-0.60	*	*	F	2.66	1.41
	Asn	309	.	.	.	.	T	T	.	1.08	-0.51	*	.	F	3.40	1.22
	Lys	310	.	.	.	.	T	T	.	0.79	0.17	*	*	F	2.16	1.16
	Gly	311	.	.	.	.	T	T	.	0.44	0.30	.	*	F	1.67	0.91

	Thr	312	.	.	.	.	.	T	C	0.44	0.34	.	*	F	1.13	0.56
	Leu	313	.	.	.	B	T	.	.	-0.11	0.73	.	.	.	0.14	0.24
	Trp	314	.	.	B	B	.	.	.	-0.32	1.37	.	.	.	-0.60	0.18
	Gly	315	.	.	B	B	.	.	.	-1.07	1.37	.	.	.	-0.60	0.20
5	Phe	316	.	.	B	B	.	.	.	-1.58	1.67	.	.	.	-0.60	0.21
	Val	317	.	.	B	B	.	.	.	-1.27	1.63	*	.	.	-0.60	0.14
	Pro	318	.	.	B	B	.	.	.	-0.46	0.71	*	.	.	-0.60	0.24
	Phe	319	.	.	B	B	.	.	.	-0.17	0.29	.	.	.	-0.30	0.49
	Val	320	.	.	.	B	.	.	C	0.18	-0.10	.	.	.	0.95	1.14
10	Asp	321	.	.	.	B	.	.	C	0.67	-0.34	.	.	F	1.40	1.28
	Glu	322	.	.	.	.	T	.	.	1.21	-0.34	.	.	F	2.10	2.28
	Gln	323	.	.	.	.	.	.	C	1.42	-0.64	.	.	F	2.50	4.44
	Gln	324	.	.	.	.	.	T	C	1.23	-1.29	.	.	F	3.00	4.60
	Pro	325	.	.	.	.	.	T	C	1.88	-0.60	.	*	F	2.70	1.86
15	Thr	326	.	.	.	.	T	T	.	0.99	-0.17	.	*	F	2.30	1.66
	Glu	327	.	.	B	.	.	T	.	0.78	0.11	.	*	F	0.85	0.67
	Ile	328	.	.	B	B	.	.	.	-0.11	0.14	*	*	F	0.15	0.67
	Pro	329	.	.	B	B	.	.	.	-0.42	0.40	.	*	.	-0.60	0.33
	Ile	330	.	.	B	B	.	.	.	-1.02	0.40	.	*	.	-0.60	0.27
20	Pro	331	.	.	B	B	.	.	.	-0.74	1.09	.	*	.	-0.60	0.32
	Ile	332	.	.	B	B	.	.	.	-1.63	0.90	.	*	.	-0.60	0.28
	Thr	333	.	.	B	B	.	.	.	-1.09	1.16	.	*	.	-0.60	0.28
	Leu	334	.	.	B	B	.	.	.	-0.88	0.90	.	*	.	-0.60	0.18
	His	335	.	.	B	B	.	.	.	-0.23	0.47	.	*	.	-0.60	0.43
25	Ile	336	.	.	B	.	.	T	.	-0.02	0.54	.	*	.	-0.20	0.47
	Gly	337	.	.	B	.	.	T	.	0.27	0.46	.	*	.	0.05	0.91
	Asp	338	.	.	.	.	T	T	.	0.58	0.39	.	*	.	1.00	0.66
	Tyr	339	.	.	B	.	.	T	.	1.04	-0.11	.	*	.	1.60	1.58
	Asn	340	.	.	.	.	T	T	.	0.83	-0.37	*	*	.	2.25	1.58
30	Met	341	.	.	.	.	T	T	.	1.51	-0.04	*	*	.	2.50	1.48
	Asp	342	.	.	.	.	T	T	.	1.86	0.39	*	*	F	1.80	1.46
	Gly	343	.	.	.	.	.	T	C	1.27	-0.37	*	*	F	1.95	1.52
	Tyr	344	.	.	.	.	.	T	C	0.70	-0.27	.	*	F	1.70	1.55
	Pro	345	A	.	.	.	.	T	.	-0.16	-0.20	.	*	F	1.10	0.76
35	Asp	346	A	.	.	.	.	T	.	-0.44	0.44	*	.	F	-0.05	0.57
	Ala	347	A	.	.	.	.	T	.	-1.26	0.70	*	*	.	-0.20	0.26
	Leu	348	.	.	B	B	.	.	.	-0.87	0.63	*	.	.	-0.60	0.14
	Val	349	.	.	B	B	.	.	.	-0.62	0.20	*	.	.	-0.30	0.16
	Ile	350	.	.	B	B	.	.	.	-0.72	0.60	.	.	.	-0.60	0.26
40	Leu	351	.	.	B	B	.	.	.	-1.02	0.59	.	.	.	-0.30	0.46
	Lys	352	.	.	B	B	.	.	.	-0.78	0.29	.	.	F	0.45	0.82
	Asn	353	.	.	.	.	.	T	C	-0.27	0.07	.	.	F	1.50	1.16
	Thr	354	.	.	.	.	.	T	C	0.59	-0.23	.	.	F	2.40	1.89
	Ser	355	.	.	.	.	.	T	C	1.48	-0.51	*	.	F	3.00	1.52
45	Gly	356	.	.	.	.	.	T	C	2.29	-0.11	*	.	F	2.40	1.64
	Ser	357	.	.	.	.	.	.	C	1.66	-0.11	.	.	F	1.90	1.97
	Asn	358	.	A	.	.	.	.	C	0.96	-0.10	.	.	F	1.40	1.48
	Gln	359	.	A	B	.	.	.	.	0.46	0.30	.	.	F	0.30	1.30
	Gln	360	.	A	B	.	.	.	.	-0.06	0.56	.	.	F	-0.45	0.80
50	Ala	361	.	A	B	.	.	.	.	0.29	0.86	.	.	.	-0.60	0.41
	Phe	362	.	A	B	.	.	.	.	0.59	0.46	.	.	.	-0.60	0.41
	Leu	363	.	A	B	.	.	.	.	-0.27	0.46	.	.	.	-0.60	0.38
	Leu	364	.	A	B	.	.	.	.	-0.48	0.70	.	.	.	-0.60	0.28
	Glu	365	.	A	B	.	.	.	.	-1.14	0.63	.	.	.	-0.60	0.50
55	Asn	366	.	A	.	.	T	.	.	-0.56	0.41	.	.	.	-0.20	0.32
	Val	367	.	.	.	.	.	T	C	0.14	0.13	.	.	.	0.30	0.63
	Pro	368	.	.	.	.	T	T	.	0.37	-0.16	.	.	.	1.10	0.59
	Cys	369	.	.	.	.	T	T	.	0.88	0.34	.	.	.	0.50	0.37
	Asn	370	.	.	.	.	T	T	.	0.21	0.33	.	.	.	0.50	0.67
60	Asn	371	.	.	.	.	.	T	C	0.21	0.26	.	.	.	0.30	0.23
	Ala	372	.	.	.	.	.	T	C	1.07	-0.17	.	.	.	0.90	0.75
	Ser	373	A	.	.	.	.	T	.	0.69	-0.74	*	.	.	1.00	0.80
	Cys	374	A	.	.	.	.	T	.	1.47	-0.64	*	.	.	1.00	0.50

	Glu	375	A	A	.	.	.	.	.	1.58	-1.04	*	.	F	0.75	0.98
	Glu	376	A	A	.	.	.	.	.	0.98	-1.54	*	.	F	0.90	1.43
	Ala	377	A	A	.	.	.	.	.	0.87	-1.31	*	.	F	0.90	2.64
	Arg	378	A	A	.	.	.	.	.	1.21	-1.10	*	*	F	0.90	1.32
5	Arg	379	A	A	.	.	.	.	.	1.02	-1.10	*	*	.	0.75	1.52
	Met	380	A	A	.	.	.	.	.	0.78	-0.46	*	*	.	0.45	1.12
	Phe	381	A	A	.	.	.	.	.	0.49	-0.20	*	*	.	0.30	0.89
	Lys	382	A	A	.	.	.	.	.	1.08	0.71	*	*	.	-0.60	0.48
	Val	383	A	A	.	.	.	.	.	0.16	0.71	*	*	.	-0.60	0.84
10	Tyr	384	.	A	B	.	.	.	.	-0.27	0.79	*	*	.	-0.60	0.80
	Trp	385	.	A	B	.	.	.	.	0.33	0.49	*	*	.	-0.60	0.58
	Glu	386	A	A	.	.	.	.	.	0.22	0.49	*	*	.	-0.45	1.30
	Leu	387	A	A	.	.	.	.	.	0.18	0.53	*	*	.	-0.60	0.68
	Thr	388	A	A	.	.	.	.	.	1.03	0.17	*	.	F	0.00	1.05
15	Asp	389	A	A	.	.	.	.	.	0.39	-0.34	.	.	F	0.60	1.05
	Leu	390	A	A	.	.	.	.	.	0.72	0.34	.	.	F	-0.15	0.89
	Asn	391	A	A	.	.	.	.	.	0.72	-0.34	*	.	F	0.60	1.23
	Gln	392	A	A	.	.	.	.	.	0.94	-0.83	*	.	F	0.90	1.23
	Ile	393	A	A	.	.	.	.	.	0.66	-0.33	*	.	F	0.60	1.51
20	Lys	394	A	A	.	.	.	.	.	-0.20	-0.40	*	.	F	0.45	0.93
	Asp	395	A	A	.	.	.	.	.	0.02	-0.16	*	.	.	0.30	0.40
	Ala	396	A	A	.	.	.	.	.	-0.29	-0.06	*	.	.	0.30	0.57
	Met	397	.	A	B	.	.	.	.	-0.99	-0.26	.	.	.	0.30	0.41
	Val	398	A	A	.	.	.	.	.	-0.80	0.53	.	.	.	-0.60	0.21
25	Ala	399	A	A	.	.	.	.	.	-0.84	1.31	.	.	.	-0.60	0.18
	Thr	400	A	A	.	.	.	.	.	-1.73	0.81	*	.	.	-0.60	0.31
	Phe	401	A	A	.	.	.	.	.	-1.39	0.89	*	.	.	-0.60	0.29
	Phe	402	A	A	.	.	.	.	.	-0.79	1.00	*	.	.	-0.60	0.46
	Asp	403	A	A	.	.	.	.	.	0.07	0.50	*	.	.	-0.60	0.55
30	Ile	404	A	A	.	.	.	.	.	0.31	0.01	*	.	.	-0.15	1.05
	Tyr	405	A	.	.	.	.	T	.	-0.27	-0.34	*	.	.	0.85	1.20
	Glu	406	A	.	.	.	.	T	.	-0.38	-0.44	*	*	.	0.70	0.51
	Asp	407	A	.	.	.	.	T	.	0.32	0.24	*	*	.	0.10	0.59
	Gly	408	A	.	.	.	.	T	.	-0.57	-0.44	*	*	.	0.70	0.63
35	Ile	409	A	.	.	B	.	.	.	-0.53	-0.51	.	*	.	0.60	0.26
	Leu	410	A	.	.	B	.	.	.	-1.14	0.13	*	.	.	-0.30	0.11
	Asp	411	.	.	B	B	.	.	.	-1.96	0.77	.	.	.	-0.60	0.09
	Ile	412	.	.	B	B	.	.	.	-2.26	1.03	*	*	.	-0.60	0.10
	Val	413	.	.	B	B	.	.	.	-1.87	0.73	.	.	.	-0.60	0.16
40	Val	414	.	.	B	B	.	.	.	-1.32	0.04	.	.	.	-0.30	0.20
	Leu	415	.	.	B	B	.	.	.	-0.76	0.47	.	*	.	-0.26	0.28
	Ser	416	.	.	B	.	.	T	.	-1.07	0.54	*	*	F	0.63	0.58
	Lys	417	.	.	.	.	T	T	.	-0.13	0.39	*	.	F	1.82	1.13
	Gly	418	.	.	.	.	T	T	.	0.72	-0.26	.	.	F	2.76	2.75
45	Tyr	419	.	.	.	.	T	T	.	1.58	-0.54	.	*	F	3.40	3.30
	Thr	420	.	.	.	.	.	T	C	1.69	-0.93	.	.	F	2.86	2.76
	Lys	421	.	.	.	.	.	T	C	1.40	-0.14	.	*	F	2.22	2.41
	Asn	422	.	.	B	.	.	T	.	0.47	-0.07	.	*	F	1.68	1.55
	Asp	423	A	.	.	.	.	T	.	0.78	-0.14	.	*	F	1.19	0.75
50	Phe	424	A	A	.	.	.	.	.	0.71	-0.13	.	*	.	0.30	0.51
	Ala	425	A	A	B	.	.	.	.	0.21	0.36	.	*	.	-0.30	0.46
	Ile	426	A	A	.	.	.	.	.	0.21	0.64	.	*	.	-0.60	0.23
	His	427	A	A	.	.	.	.	.	0.21	0.64	*	.	.	-0.60	0.53
	Thr	428	A	A	.	.	.	.	.	0.21	0.26	*	*	.	-0.06	0.84
55	Leu	429	A	.	.	.	.	T	C	0.21	0.16	*	*	.	0.93	1.92
	Lys	430	.	.	.	.	.	T	C	0.80	0.26	*	*	F	1.32	1.22
	Asn	431	.	.	.	.	.	T	C	1.10	-0.24	*	*	F	2.16	1.47
	Asn	432	.	.	.	.	.	T	C	1.13	-0.23	.	*	F	2.40	1.80
	Phe	433	A	A	.	.	.	.	.	0.86	-0.91	.	*	.	1.71	1.50
60	Glu	434	A	A	.	.	.	.	.	1.42	-0.41	.	*	.	1.02	0.94
	Ala	435	A	A	.	.	.	.	.	0.68	-0.06	.	*	.	0.78	0.92
	Asp	436	A	A	.	.	.	.	.	-0.18	0.33	.	*	.	-0.06	0.92
	Ala	437	A	.	.	B	.	.	.	-0.13	0.19	.	*	.	-0.30	0.39

	Tyr	438	A	.	.	B	.	.	.	-0.29	0.19	*	*	.	-0.30	0.78
	Phe	439	A	.	.	B	.	.	.	-1.18	0.33	*	*	.	-0.30	0.35
	Val	440	A	.	.	B	.	.	.	-1.44	1.01	.	.	.	-0.60	0.24
	Lys	441	.	.	B	B	.	.	.	-2.26	1.16	.	.	.	-0.60	0.11
	Val	442	.	.	B	B	.	.	.	-1.97	1.09	*	.	.	-0.60	0.11
	Ile	443	.	.	B	B	.	.	.	-2.07	0.69	.	.	.	-0.60	0.20
	Val	444	.	.	B	B	.	.	.	-2.18	0.47	.	.	.	-0.60	0.10
	Leu	445	.	.	B	.	.	T	.	-1.99	1.16	.	.	.	-0.20	0.11
	Ser	446	.	.	B	.	.	T	.	-2.33	1.09	.	.	.	-0.20	0.08
	Gly	447	.	.	.	.	T	T	.	-1.48	0.79	.	.	.	0.20	0.15
	Leu	448	.	.	.	.	T	T	.	-0.59	0.54	.	.	.	0.54	0.29
	Cys	449	.	.	.	.	T	T	.	-0.40	-0.14	.	.	.	1.78	0.36
	Ser	450	.	.	.	.	T	T	.	0.20	0.04	.	.	F	1.67	0.20
	Asn	451	.	.	.	.	T	T	.	0.61	0.04	*	.	F	2.01	0.37
	Asp	452	.	.	.	.	T	T	.	1.00	-0.64	*	.	F	3.40	1.34
	Cys	453	.	.	B	.	.	T	.	0.92	-1.21	*	.	F	2.66	2.00
	Pro	454	.	.	.	.	T	T	.	1.28	-0.91	*	.	F	2.57	0.87
	Arg	455	.	.	.	.	T	T	.	1.37	-0.83	*	.	F	2.23	0.75
	Lys	456	.	.	B	.	.	T	.	0.67	-0.40	*	.	F	1.34	2.17
	Ile	457	.	.	B	.	.	.	.	0.32	-0.19	*	.	F	0.80	1.22
	Thr	458	.	.	B	.	.	T	.	0.13	-0.19	*	.	F	0.85	0.61
	Pro	459	.	.	B	.	.	T	.	0.34	0.46	*	.	F	-0.05	0.23
	Phe	460	.	.	B	.	.	T	.	0.23	0.86	*	.	.	-0.20	0.52
	Gly	461	.	.	B	.	.	T	.	-0.02	0.57	.	.	.	-0.20	0.63
	Val	462	.	.	B	.	.	.	.	0.52	0.51	.	.	F	-0.25	0.63
	Asn	463	.	.	.	.	.	.	C	0.62	0.51	.	.	F	-0.05	0.72
	Gln	464	.	.	.	.	.	T	C	0.59	0.16	.	.	F	0.60	1.12
	Pro	465	.	.	.	.	.	T	C	0.40	0.49	.	.	F	0.30	2.37
	Gly	466	.	.	.	.	.	T	C	0.14	0.53	*	.	F	0.30	1.03
	Pro	467	.	.	.	.	.	T	C	0.76	0.74	*	.	F	0.15	0.59
	Tyr	468	.	.	B	B	.	.	.	0.44	1.10	.	.	.	-0.60	0.60
	Ile	469	.	.	B	B	.	.	.	0.13	1.16	.	.	.	-0.60	0.87
	Met	470	.	.	B	B	.	.	.	-0.51	1.21	.	.	.	-0.60	0.81
	Tyr	471	.	.	B	B	.	.	.	-0.17	1.43	.	.	.	-0.60	0.39
	Thr	472	.	.	B	B	.	.	.	-0.54	0.67	.	*	.	-0.60	0.92
	Thr	473	.	.	B	B	.	.	.	-0.30	0.49	.	*	.	-0.60	0.94
	Val	474	.	.	B	B	.	.	.	0.24	0.27	.	*	.	-0.30	0.96
	Asp	475	.	.	B	.	.	T	.	0.60	-0.06	.	*	F	0.85	0.66
	Ala	476	.	.	B	.	.	T	.	0.03	0.21	.	*	F	0.25	0.72
	Asn	477	.	.	B	.	.	T	.	0.39	0.41	.	*	.	-0.20	0.80
	Gly	478	.	.	B	.	.	T	.	0.70	-0.23	.	*	.	0.70	0.95
	Tyr	479	.	.	B	.	.	.	.	1.21	0.17	.	*	F	0.20	1.52
	Leu	480	.	.	B	.	.	T	.	0.91	0.10	*	*	F	0.46	0.93
	Lys	481	.	.	B	.	T	T	.	0.91	0.09	*	*	F	1.22	1.26
	Asn	482	.	.	.	.	T	T	.	0.57	0.16	.	.	F	1.28	0.81
	Gly	483	.	.	.	.	T	T	.	0.91	-0.17	.	.	F	2.09	0.98
	Ser	484	.	.	.	.	.	T	C	0.34	-0.46	.	.	F	2.10	0.85
	Ala	485	.	.	B	.	.	T	.	0.86	0.23	.	.	F	1.09	0.43
	Gly	486	.	.	B	.	.	T	.	0.81	0.21	.	.	F	0.88	0.59
	Gln	487	.	.	B	.	.	T	.	0.51	0.19	.	.	F	0.67	0.76
	Leu	488	.	.	B	.	.	.	.	0.27	0.19	*	.	F	0.41	1.01
	Ser	489	.	.	B	.	.	T	.	0.53	0.19	.	*	F	0.40	1.03
	Gln	490	.	.	B	.	.	T	.	0.31	0.26	*	.	F	0.25	0.81
	Ser	491	A	.	.	.	.	T	.	0.07	0.54	*	*	F	-0.05	0.81
	Ala	492	A	.	.	.	.	T	.	-0.74	0.36	*	*	.	0.10	0.61
	His	493	.	A	B	.	.	.	.	0.07	0.66	*	*	.	-0.60	0.29
	Leu	494	.	A	B	.	.	.	.	-0.44	0.66	*	*	.	-0.60	0.37
	Ala	495	.	A	B	.	.	.	.	-0.66	0.96	*	*	.	-0.60	0.31
	Leu	496	.	A	B	.	.	.	.	-0.60	0.89	.	*	.	-0.60	0.35
	Gln	497	.	A	B	.	.	.	.	-0.01	1.14	*	*	.	-0.60	0.66
	Leu	498	.	.	B	.	.	T	.	-0.83	0.86	*	*	.	-0.05	1.05
	Pro	499	.	.	B	.	.	T	.	-0.83	1.00	*	*	.	-0.20	0.95
	Tyr	500	.	.	B	.	.	T	.	-0.59	1.00	*	*	.	-0.20	0.45

	Asn	501	.	.	B	.	.	T	.	-0.59	1.03	*	*	.	-0.20	0.54
	Val	502	.	.	B	.	.	.	.	-0.93	1.03	*	*	.	-0.40	0.29
	Leu	503	.	.	B	.	.	.	.	-0.01	1.03	*	*	.	-0.40	0.18
	Gly	504	.	.	B	.	.	.	.	-0.10	0.27	*	.	.	-0.10	0.22
5	Leu	505	.	.	B	.	.	.	.	-0.44	0.26	*	.	.	-0.10	0.40
	Gly	506	.	.	B	.	.	.	.	-0.44	0.11	*	.	F	0.05	0.49
	Arg	507	.	.	B	.	.	.	.	-0.29	-0.17	*	.	F	0.65	0.80
	Ser	508	.	.	.	.	.	T	C	-0.29	0.19	*	.	F	0.45	0.84
	Ala	509	.	.	B	.	.	T	.	0.06	0.19	*	.	F	0.25	0.70
10	Asn	510	.	.	B	.	.	T	.	0.83	-0.24	*	.	.	0.70	0.60
	Phe	511	.	.	B	.	.	T	.	0.37	0.26	*	.	.	0.10	0.60
	Leu	512	.	.	B	.	.	.	.	0.01	0.56	*	.	.	-0.40	0.49
	Asp	513	.	.	B	.	.	.	.	-0.54	0.81	*	.	.	-0.40	0.48
	His	514	.	.	B	B	.	.	.	-0.30	1.06	*	*	.	-0.60	0.41
15	Leu	515	.	.	B	B	.	.	.	-1.19	0.70	*	.	.	-0.60	0.49
	Tyr	516	.	.	B	B	.	.	.	-0.70	0.70	*	.	.	-0.60	0.21
	Val	517	.	.	B	B	.	.	.	0.22	1.13	*	.	.	-0.60	0.24
	Gly	518	.	.	B	B	.	.	.	0.01	0.63	*	.	.	-0.60	0.56
	Ile	519	.	.	B	B	.	.	.	-0.26	0.37	*	.	.	0.04	0.55
20	Pro	520	.	.	B	B	.	.	.	0.21	0.00	*	*	F	0.53	1.00
	Arg	521	.	.	.	.	.	T	C	0.46	-0.21	*	.	F	2.07	1.00
	Pro	522	.	.	.	.	.	T	C	1.36	-0.64	.	.	F	2.86	2.47
	Ser	523	.	.	.	.	T	T	.	1.40	-1.33	.	*	F	3.40	3.19
	Gly	524	.	.	.	.	.	T	C	1.40	-1.37	*	*	F	2.86	2.18
25	Glu	525	.	.	.	.	T	.	.	1.72	-0.69	*	*	F	2.37	0.99
	Lys	526	.	.	.		.	.	C	1.66	-1.11	*	*	F	1.98	1.45
	Ser	527	.	.	B	.	.	.	.	1.87	-1.50	*	.	F	1.44	2.92
	Ile	528	.	A	B	.	.	.	.	2.17	-1.53	*	.	F	0.90	2.92
	Arg	529	A	A	.	.	.	.	.	2.22	-1.53	*	.	F	0.90	2.53
30	Lys	530	A	A	.	.	.	.	.	1.91	-0.61	*	.	F	0.90	1.98
	Gln	531	A	A	.	.	.	.	.	1.28	-0.51	*	.	F	0.90	4.09
	Glu	532	A	A	.	.	.	.	.	0.69	-0.70	.	.	F	0.90	2.11
	Trp	533	.	A	B	B	.	.	.	0.69	-0.01	.	.	.	0.30	0.74
	Thr	534	.	A	B	B	.	.	.	0.37	0.67	.	.	.	-0.60	0.30
35	Ala	535	.	A	B	B	.	.	.	0.32	0.70	.	.	.	-0.60	0.27
	Ile	536	.	A	B	B	.	.	.	0.02	1.10	*	.	.	-0.60	0.41
	Ile	537	.	.	B	.	.	T	.	0.02	0.57	.	.	.	-0.20	0.38
	Pro	538	.	.	.	.	.	T	C	-0.50	0.49	.	.	F	0.15	0.65
	Asn	539	.	.	.	.	T	T	.	-1.08	0.67	.	.	F	0.35	0.76
40	Ser	540	.	.	.	.	T	T	.	-1.34	0.67	.	.	F	0.35	0.76
	Gln	541	.	.	B	B	.	.	.	-1.34	0.63	.	.	F	-0.45	0.37
	Leu	542	.	.	B	B	.	.	.	-0.67	0.89	.	.	.	-0.60	0.16
	Ile	543	.	.	B	B	.	.	.	-0.70	0.91	.	.	.	-0.60	0.18
	Val	544	.	.	B	B	.	.	.	-0.91	1.29	.	.	.	-0.60	0.17
45	Ile	545	.	.	B	B	.	.	.	-0.64	1.31	.	.	.	-0.60	0.31
	Pro	546	.	.	B	.	.	.	.	-0.64	1.13	.	.	.	-0.40	0.61
	Tyr	547	.	.	B	.	.	T	.	-0.69	0.84	.	.	.	-0.05	1.32
	Pro	548	.	.	.	.	T	T	.	-0.01	0.84	*	.	.	0.35	1.39
	His	549	.	.	.	.	T	T	.	0.96	0.59	*	.	.	0.35	1.39
50	Asn	550	.	.	.	.	.	T	C	1.54	0.16	*	.	.	0.45	1.74
	Val	551	.	.	B	.	.	.	.	1.47	-0.21	*	.	.	0.65	1.51
	Pro	552	.	.	.	.	.	T	C	1.41	0.27	*	.	F	0.60	1.17
	Arg	553	.	.	.	.	T	T	.	1.03	0.16	*	.	F	0.65	0.97
	Ser	554	.	.	.	.	T	T	.	1.11	0.26	*	*	F	0.80	1.32
55	Trp	555	.	.	.	.	T	T	.	0.30	-0.39	*	*	.	1.25	1.71
	Ser	556	.	A	B	.	.	.	.	0.91	-0.13	*	*	.	0.30	0.72
	Ala	557	.	A	B	.	.	.	.	0.31	0.63	.	*	.	-0.60	0.84
	Lys	558	.	A	B	.	.	.	.	-0.11	0.93	.	*	.	-0.60	0.66
	Leu	559	.	A	B	.	.	.	.	-0.02	0.50	.	*	.	-0.60	0.71
60	Tyr	560	.	.	B	.	.	.	.	-0.03	0.54	.	*	.	-0.25	1.09
	Leu	561	.	.	B	.	.	.	.	0.27	0.43	.	*	.	-0.40	0.73
	Thr	562	.	.	B	.	.	T	.	-0.03	0.83	*	*	F	0.10	1.42
	Pro	563	.	.	B	.	.	T	.	-0.93	0.83	*	*	F	-0.05	0.64

	Ser	564	.	.	B	.	.	T	.	-0.93	0.71	.	.	F	-0.05	0.57
	Asn	565	.	.	B	.	.	T	.	-1.50	0.71	.	.	F	-0.05	0.33
	Ile	566	.	.	B	B	.	.	.	-1.00	0.91	.	.	.	-0.60	0.17
	Val	567	.	.	B	B	.	.	.	-1.28	0.97	.	.	.	-0.60	0.19
	Leu	568	.	.	B	B	.	.	.	-1.96	1.09	.	.	.	-0.60	0.12
	Leu	569	.	.	B	B	.	.	.	-2.24	1.37	.	.	.	-0.60	0.12
	Thr	570	.	.	B	B	.	.	.	-3.06	1.19	.	.	.	-0.60	0.16
	Ala	571	.	.	B	B	.	.	.	-3.06	1.23	.	.	.	-0.60	0.16
	Ile	572	A	.	.	B	.	.	.	-2.54	1.23	.	.	.	-0.60	0.14
	Ala	573	A	.	.	B	.	.	.	-2.59	0.97	.	.	.	-0.60	0.09
	Leu	574	.	.	B	B	.	.	.	-2.44	1.13	.	.	.	-0.60	0.07
	Ile	575	.	.	B	B	.	.	.	-2.99	1.20	.	.	.	-0.60	0.05
	Gly	576	.	.	B	B	.	.	.	-3.10	1.16	.	.	.	-0.60	0.04
	Val	577	.	.	B	B	.	.	.	-3.10	1.44	.	.	.	-0.60	0.04
	Cys	578	.	.	B	B	.	.	.	-3.32	1.44	.	.	.	-0.60	0.04
	Val	579	.	.	B	B	.	.	.	-3.10	1.44	.	.	.	-0.60	0.03
	Phe	580	.	.	B	B	.	.	.	-3.10	1.51	.	.	.	-0.60	0.05
	Ile	581	.	.	B	B	.	.	.	-3.64	1.56	.	.	.	-0.60	0.06
	Leu	582	.	.	B	B	.	.	.	-3.13	1.67	.	.	.	-0.60	0.06
	Ala	583	A	.	B	B	.	.	.	-3.36	1.46	.	.	.	-0.60	0.07
	Ile	584	A	.	.	B	.	.	.	-3.31	1.36	.	.	.	-0.60	0.07
	Ile	585	A	.	.	B	.	.	.	-2.64	1.36	*	.	.	-0.60	0.07
	Gly	586	A	.	.	B	.	.	.	-2.04	1.17	.	.	.	-0.60	0.09
	Ile	587	A	.	.	B	.	.	.	-1.23	1.59	.	.	.	-0.60	0.13
	Leu	588	A	.	.	B	.	.	.	-0.64	1.30	*	.	.	-0.60	0.32
	His	589	A	.	.	B	.	.	.	0.29	0.61	.	.	.	-0.60	0.57
	Trp	590	A	.	.	B	.	.	.	1.22	0.19	.	.	.	-0.15	1.62
	Gln	591	A	.	.	B	.	.	.	0.98	-0.50	*	.	F	0.60	3.93
	Glu	592	A	.	.	B	.	.	.	1.87	-0.69	*	.	F	0.90	2.92
	Lys	593	A	.	.	.	.	.	.	2.68	-1.19	.	*	F	1.10	4.64
	Lys	594	A	.	.	.	.	.	.	2.82	-2.10	.	.	F	1.10	4.47
	Ala	595	A	.	.	.	.	.	.	3.11	-2.50	.	*	F	1.10	5.06
	Asp	596	A	.	.	.	.	T	.	3.16	-2.50	*	.	F	1.30	4.38
	Asp	597	A	.	.	.	.	T	.	3.27	-2.50	*	*	F	1.30	4.38
	Arg	598	A	.	.	.	.	T	.	3.22	-2.50	*	.	F	1.30	8.49
	Glu	599	A	.	.	.	.	T	.	3.18	-2.60	*	*	F	1.30	8.81
	Lys	600	A	A	.	.	.	.	.	3.18	-2.60	.	.	F	0.90	9.13
	Arg	601	A	A	.	.	.	.	.	3.14	-2.10	*	.	F	0.90	4.71
	Gln	602	A	A	.	.	.	.	.	3.26	-1.60	*	.	F	0.90	3.70
	Glu	603	A	A	.	.	.	.	.	2.44	-1.60	*	.	F	0.90	3.63
	Ala	604	A	A	.	.	.	.	.	2.41	-0.81	.	*	.	0.75	1.60
	His	605	A	A	.	.	.	.	.	1.67	-0.31	.	*	.	0.45	1.26
	Arg	606	A	A	.	.	.	.	.	1.56	0.07	*	*	.	-0.30	0.63
	Phe	607	A	A	.	.	.	.	.	0.97	0.07	*	*	.	-0.15	1.04
	His	608	A	A	.	.	.	.	.	0.37	0.07	*	*	.	-0.30	0.77
	Phe	609	A	A	.	.	.	.	.	0.57	0.19	*	*	.	-0.30	0.39
	Asp	610	A	A	.	.	.	.	.	0.21	0.61	*	*	.	-0.60	0.58
	Ala	611	A	A	.	.	.	.	.	-0.29	0.26	*	*	.	-0.30	0.54
	Met	612	A	A	.	.	.	.	.	0.02	0.19	.	*	.	-0.30	0.80

Table 7

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	.	.	.	.	.	.	C	0.09	0.10	.	.	.	0.46	0.66
Ser	2	.	.	.	.	.	T	C	0.48	0.16	.	.	.	0.84	0.74
Ser	3	.	.	.	.	.	T	C	0.06	-0.27	*	.	.	1.77	1.01
Gly	4	.	.	.	.	.	T	C	-0.37	-0.01	.	.	.	1.80	0.84
Thr	5	.	.	.	.	.	T	C	-0.27	0.06	.	.	F	1.17	0.52
Glu	6	A	.	.	.	.	.	.	0.12	0.59	*	.	F	0.29	0.41
Leu	7	A	.	.	.	.	.	.	0.08	0.63	.	.	.	-0.04	0.63
Leu	8	A	.	.	.	.	.	.	-0.21	0.63	.	.	.	-0.22	0.43
Trp	9	A	.	.	.	.	T	.	-0.46	0.64	.	.	.	-0.20	0.25
Pro	10	A	.	.	.	.	T	.	-0.96	1.14	.	.	.	-0.20	0.31
Gly	11	A	.	.	.	.	T	.	-1.77	1.14	.	.	.	-0.20	0.31
Ala	12	A	.	.	.	.	T	.	-1.81	1.14	.	.	.	-0.20	0.24
Ala	13	A	.	.	B	.	.	.	-1.81	0.87	.	.	.	-0.60	0.12
Leu	14	A	.	.	B	.	.	.	-2.33	1.13	.	.	.	-0.60	0.10
Leu	15	A	.	.	B	.	.	.	-2.47	1.39	.	.	.	-0.60	0.08
Val	16	A	.	.	B	.	.	.	-2.98	1.31	.	.	.	-0.60	0.08
Leu	17	A	.	.	B	.	.	.	-2.98	1.46	.	.	.	-0.60	0.07
Leu	18	A	.	.	B	.	.	.	-2.98	1.27	.	.	.	-0.60	0.09
Gly	19	A	.	.	B	.	.	.	-2.47	1.09	.	*	.	-0.60	0.12
Val	20	A	.	.	B	.	.	.	-2.47	0.83	.	.	.	-0.60	0.19
Ala	21	A	.	.	B	.	.	.	-2.28	0.83	.	*	.	-0.60	0.19
Ala	22	A	.	.	B	.	.	.	-2.32	0.71	*	*	.	-0.60	0.10
Ser	23	A	.	.	B	.	.	.	-1.40	0.93	*	*	.	-0.60	0.10
Leu	24	A	.	.	B	.	.	.	-1.72	0.29	.	*	.	-0.30	0.20
Cys	25	.	.	B	B	.	.	.	-1.17	0.36	*	*	.	-0.30	0.11
Val	26	.	.	B	B	.	.	.	-0.47	0.24	*	*	.	-0.30	0.11
Arg	27	.	.	.	B	T	.	.	-0.09	-0.14	*	*	.	1.04	0.25
Cys	28	.	.	.	B	T	.	.	-0.13	-0.40	*	*	.	1.38	0.73
Ser	29	.	.	.	B	T	.	.	0.09	-0.54	*	*	F	2.17	0.97
Arg	30	.	.	.	.	.	T	C	0.80	-0.69	*	.	F	2.71	0.50
Pro	31	.	.	.	.	T	T	.	1.77	-0.69	*	.	F	3.40	1.86
Gly	32	.	.	.	.	T	T	.	1.36	-1.26	*	.	F	3.06	2.72
Ala	33	.	.	.	.	.	T	C	2.02	-1.26	*	.	F	2.52	1.86
Lys	34	.	A	.	.	.	.	C	2.37	-1.26	*	*	F	1.78	2.08
Arg	35	A	A	.	.	.	.	.	1.37	-1.69	*	*	F	1.24	4.21
Ser	36	A	A	.	.	.	.	.	1.33	-1.43	*	.	F	0.90	2.92
Glu	37	A	A	.	.	.	.	.	1.68	-1.17	*	.	F	0.90	2.29
Lys	38	A	A	.	.	.	.	.	2.27	-0.77	*	.	F	0.90	2.02
Ile	39	A	A	.	.	.	.	.	2.33	-0.37	*	.	F	0.60	2.62
Tyr	40	A	.	.	.	.	.	.	1.92	-0.76	.	.	F	1.40	2.96
Gln	41	A	.	.	.	.	T	.	1.41	-0.37	.	*	F	1.60	1.98
Gln	42	A	.	.	.	.	T	.	1.52	0.31	.	.	F	1.30	2.33
Arg	43	.	.	.	.	.	T	C	1.48	-0.37	.	*	F	2.40	2.91
Ser	44	.	.	.	.	.	T	C	2.37	-1.13	.	.	F	3.00	2.91
Leu	45	.	A	.	.	.	.	C	2.61	-1.53	*	*	F	2.30	2.81
Arg	46	.	A	.	.	T	.	.	2.61	-1.53	*	.	F	2.20	2.49
Glu	47	.	A	.	.	T	.	.	2.31	-1.13	*	.	F	1.90	3.21
Asp	48	.	A	.	.	T	.	.	1.50	-1.13	*	.	F	1.60	5.22
Gln	49	.	A	.	.	T	.	.	1.49	-1.03	*	*	F	1.30	2.31
Gln	50	.	A	.	.	T	.	.	1.96	-0.54	*	*	F	1.58	1.92
Ser	51	.	A	.	.	.	.	C	1.54	-0.11	*	.	F	1.36	1.14
Phe	52	.	.	.	.	T	T	.	1.66	0.27	.	.	F	1.49	0.88
Thr	53	.	.	.	.	T	T	.	1.34	-0.13	.	.	F	2.37	1.00
Gly	54	.	.	.	.	T	T	.	1.10	-0.04	*	.	F	2.80	1.07
Ser	55	.	.	.	.	T	T	.	0.80	0.33	.	.	F	1.92	1.94
Arg	56	.	.	.	B	T	.	.	0.29	-0.07	.	.	F	1.84	1.80
Thr	57	.	.	.	B	T	.	.	0.13	0.13	.	.	F	0.96	1.50
Tyr	58	.	.	.	B	T	.	.	0.10	0.34	*	.	.	0.38	0.83
Ser	59	.	.	.	B	.	.	C	0.44	0.39	*	.	.	-0.10	0.42

	Leu	60	.	.	B	B	.	.	.	0.16	0.79	*	.	.	-0.60	0.50
	Val	61	.	.	B	B	.	.	.	-0.24	0.80	*	.	.	-0.60	0.33
	Gly	62	.	.	.	.	T	.	.	-0.14	0.96	.	.	.	0.00	0.26
	Gln	63	.	.	.	.	T	.	.	-0.24	1.00	.	.	.	0.00	0.48
5	Ala	64	.	.	.	.	.	.	C	-0.16	0.74	.	.	.	-0.20	0.64
	Trp	65	.	.	.	.	.	T	C	-0.16	0.53	.	.	F	0.15	1.00
	Pro	66	.	.	.	.	.	T	C	0.11	0.79	*	.	F	0.15	0.48
	Gly	67	.	.	.	.	.	T	C	0.46	0.89	*	.	F	0.15	0.48
	Pro	68	.	.	.	.	.	T	C	-0.14	0.39	*	.	F	0.45	0.75
10	Leu	69	.	A	.	.	.	.	C	-0.14	0.09	.	.	F	0.05	0.48
	Ala	70	.	A	.	.	.	.	C	-0.07	0.16	.	.	.	-0.10	0.49
	Asp	71	A	A	.	.	.	.	.	-0.17	0.16	.	.	.	-0.30	0.49
	Met	72	A	A	.	.	.	.	.	0.29	0.21	.	.	.	-0.30	0.86
	Ala	73	A	A	.	.	.	.	.	0.54	-0.47	.	.	.	0.45	1.67
15	Pro	74	A	.	.	.	.	T	.	1.36	-0.97	.	.	F	1.30	2.00
	Thr	75	A	.	.	.	.	T	.	1.99	-0.97	.	.	F	1.30	3.38
	Arg	76	A	.	.	.	.	T	.	1.18	-1.59	.	.	F	1.30	6.69
	Lys	77	A	.	.	.	.	T	.	0.97	-1.40	.	.	F	1.30	3.57
	Asp	78	A	A	.	.	.	.	.	1.56	-1.14	.	.	F	0.90	2.04
20	Lys	79	A	A	.	.	.	.	.	1.07	-1.23	.	.	F	0.90	1.80
	Leu	80	A	A	.	.	.	.	.	1.13	-0.44	.	.	.	0.30	0.78
	Leu	81	.	A	B	.	.	.	.	0.81	0.31	.	.	.	-0.30	0.73
	Gln	82	.	A	B	.	.	.	.	0.47	0.74	*	*	.	-0.60	0.57
	Phe	83	.	A	B	.	.	.	.	-0.34	1.13	*	*	.	-0.60	0.92
25	Tyr	84	.	.	.	.	.	T	C	-0.39	1.13	*	*	.	0.00	0.92
	Pro	85	.	.	.	.	.	T	C	0.42	0.44	*	*	.	0.00	0.92
	Ser	86	.	.	.	.	.	T	C	1.02	0.04	*	*	F	0.60	1.78
	Leu	87	.	.	.	.	.	T	C	0.43	-0.31	*	*	F	1.50	1.75
	Glu	88	.	.	.	.	.	.	C	0.83	-0.57	*	*	F	1.90	1.14
30	Asp	89	.	.	.	.	.	.	C	0.78	-0.61	.	*	F	2.20	1.14
	Pro	90	.	.	.	.	.	.	C	1.10	-0.61	.	*	F	2.50	1.86
	Ala	91	.	.	.	.	T	.	.	1.16	-1.30	.	*	F	3.00	2.10
	Ser	92	A	.	.	.	.	T	.	1.97	-0.54	.	*	F	2.50	1.97
	Ser	93	A	.	.	.	.	T	.	1.97	-0.14	.	*	F	1.90	2.21
35	Arg	94	A	.	.	.	.	T	.	1.27	-0.17	*	.	F	1.60	3.52
	Tyr	95	.	.	.	.	T	T	.	1.18	0.11	*	*	F	1.10	2.27
	Gln	96	.	.	.	.	T	.	.	1.81	0.11	*	*	F	0.94	2.27
	Asn	97	.	.	.	.	T	.	.	1.77	-0.27	*	*	F	1.88	2.32
	Phe	98	.	.	.	.	T	.	.	1.77	0.16	*	*	F	1.62	1.47
40	Ser	99	.	.	.	.	T	T	.	1.77	-0.21	*	*	F	2.76	1.13
	Lys	100	.	.	.	.	T	T	.	1.98	-0.61	*	.	F	3.40	1.38
	Gly	101	.	.	.	.	.	T	C	1.63	-0.51	*	.	F	2.86	2.17
	Ser	102	.	.	.	.	.	T	C	1.33	-0.87	*	.	F	2.82	1.60
	Arg	103	.	.	.	.	.	.	C	2.03	-0.87	*	.	F	2.58	1.07
45	His	104	.	.	.	.	.	T	C	2.33	-0.87	*	.	F	2.74	1.88
	Gly	105	.	.	.	.	.	T	C	1.70	-1.30	*	.	F	2.70	2.43
	Ser	106	.	.	.	.	.	T	C	1.80	-1.19	*	.	F	3.00	1.25
	Glu	107	A	.	.	.	.	T	.	1.21	-0.43	.	*	F	2.20	1.44
	Glu	108	A	.	.	.	.	.	.	1.10	-0.24	.	*	F	1.70	1.02
50	Ala	109	A	.	.	.	.	.	.	0.92	-0.67	.	*	.	1.55	1.27
	Tyr	110	A	.	.	.	.	.	.	0.38	-0.63	.	*	.	1.25	1.14
	Ile	111	A	.	.	.	.	.	.	0.09	0.06	.	.	.	-0.10	0.46
	Asp	112	A	.	.	.	.	.	.	-0.51	0.56	.	.	.	-0.40	0.46
	Pro	113	A	A	.	.	.	.	.	-0.51	0.67	.	*	.	-0.60	0.29
55	Ile	114	A	A	.	.	.	.	.	-0.17	-0.09	.	.	.	0.30	0.72
	Ala	115	A	A	.	.	.	.	.	-0.17	-0.01	*	.	.	0.30	0.67
	Met	116	A	A	.	.	.	.	.	0.72	0.74	*	.	.	-0.60	0.68
	Glu	117	A	A	.	.	.	.	.	0.43	0.71	*	.	.	-0.45	1.57
	Tyr	118	A	.	.	.	.	T	.	0.30	0.94	*	*	.	-0.05	1.63
60	Tyr	119	.	.	.	.	T	T	.	1.30	0.87	*	*	.	0.35	1.63
	Asn	120	.	.	.	.	T	T	.	1.19	0.26	*	*	.	0.65	1.84
	Trp	121	.	.	.	.	T	T	.	1.49	1.04	*	*	.	0.35	1.02
	Gly	122	.	.	.	.	T	.	.	1.53	0.67	*	.	.	0.00	0.87

	Arg	123	.	.	.	.	T	.	.	1.57	-0.09	*	.	.	1.05	1.08
	Phe	124	.	.	.	.	T	.	.	1.60	-0.06	*	.	F	1.20	1.59
	Ser	125	.	.	.	.	.	.	C	1.60	-0.54	*	.	F	1.64	2.49
	Lys	126	.	.	.	.	.	.	C	1.89	-0.97	*	*	F	1.98	2.20
5	Pro	127	.	.	.	.	.	T	C	2.23	-0.97	*	*	F	2.52	4.25
	Pro	128	.	.	.	.	.	T	C	2.12	-1.76	*	*	F	2.86	5.29
	Glu	129	.	.	.	.	T	T	.	2.23	-2.14	.	.	F	3.40	4.42
	Asp	130	A	.	.	.	.	T	.	2.53	-1.64	.	*	F	2.66	2.89
	Asp	131	A	.	.	.	.	.	.	2.19	-1.67	.	*	F	2.12	3.00
10	Asp	132	A	.	.	.	.	T	.	2.16	-1.71	.	.	F	1.98	2.32
	Ala	133	A	.	.	.	.	T	.	2.37	-0.96	.	.	F	1.64	2.18
	Asn	134	A	.	.	.	.	T	.	2.37	-0.96	.	.	F	1.30	2.26
	Ser	135	A	.	.	.	.	T	.	1.51	-0.56	*	.	F	1.30	2.18
	Tyr	136	A	.	.	.	.	.	.	0.70	0.09	*	.	F	0.20	1.60
15	Glu	137	A	.	.	.	.	.	.	-0.19	0.27	.	*	.	-0.10	0.82
	Asn	138	A	.	.	B	.	.	.	-0.27	0.56	.	.	.	-0.60	0.43
	Val	139	A	.	.	B	.	.	.	-0.22	0.74	.	.	.	-0.60	0.15
	Leu	140	A	.	.	B	.	.	.	0.08	-0.01	.	.	.	0.30	0.17
	Ile	141	A	.	.	B	.	.	.	0.37	0.39	.	.	.	-0.30	0.18
20	Cys	142	A	.	.	B	.	.	.	0.06	-0.01	.	.	.	0.56	0.49
	Lys	143	A	.	.	B	.	.	.	-0.26	-0.17	.	.	F	0.97	0.86
	Gln	144	A	.	.	.	.	.	.	0.60	-0.37	.	.	F	1.58	1.77
	Lys	145	.	.	.	.	.	.	C	1.10	-1.06	.	.	F	2.34	5.73
	Thr	146	.	.	.	.	.	.	C	1.64	-1.14	.	.	F	2.60	4.13
25	Thr	147	.	.	.	.	.	.	C	1.72	-0.71	.	*	F	2.34	2.36
	Glu	148	.	.	.	.	.	.	C	1.68	-0.61	.	.	F	2.08	1.19
	Thr	149	.	.	.	.	.	.	C	1.68	-0.21	.	.	F	1.52	1.43
	Gly	150	.	A	.	.	.	.	C	1.63	-0.30	.	.	F	1.06	1.72
	Ala	151	A	A	.	.	.	.	.	1.60	-0.79	.	.	F	0.90	1.72
30	Gln	152	A	A	.	.	.	.	.	1.02	-0.36	.	.	F	0.60	1.18
	Gln	153	A	A	.	.	.	.	.	0.68	-0.16	.	.	F	0.45	0.83
	Glu	154	.	A	.	.	T	.	.	0.64	-0.16	.	.	F	0.85	0.82
	Gly	155	.	.	.	.	T	T	.	0.18	-0.23	.	.	F	1.25	0.47
	Ile	156	.	.	.	.	T	T	.	0.10	0.06	*	*	F	0.65	0.22
35	Gly	157	.	.	.	.	T	T	.	0.21	0.23	*	*	F	0.90	0.07
	Gly	158	.	.	.	.	T	T	.	-0.13	0.23	*	*	F	1.15	0.14
	Leu	159	.	.	.	.	.	.	C	-0.13	0.23	*	*	.	0.85	0.19
	Cys	160	.	.	B	.	.	T	.	-0.60	-0.46	*	*	.	1.70	0.32
	Arg	161	.	.	.	.	T	T	.	-0.01	-0.20	*	*	F	2.50	0.27
40	Gly	162	.	.	.	.	T	T	.	-0.48	-0.24	.	*	F	2.25	0.44
	Asp	163	.	.	.	.	T	T	.	-0.43	-0.24	.	*	F	2.00	0.68
	Leu	164	A	A	.	.	.	.	.	-0.43	-0.43	.	*	F	0.95	0.46
	Ser	165	A	A	.	.	.	.	.	-0.36	0.26	.	*	.	-0.05	0.39
	Leu	166	A	A	.	.	.	.	.	-1.28	0.33	*	*	.	-0.30	0.23
45	Ser	167	A	A	.	.	.	.	.	-0.89	1.01	.	*	.	-0.60	0.23
	Leu	168	A	A	.	.	.	.	.	-1.20	0.33	.	*	.	-0.30	0.35
	Ala	169	A	A	.	.	.	.	.	-0.73	0.43	.	*	.	-0.60	0.61
	Leu	170	A	A	.	.	.	.	.	-0.64	0.17	*	*	.	-0.05	0.45
	Lys	171	.	A	.	.	T	.	.	-0.14	0.21	*	*	F	0.75	0.84
50	Thr	172	.	A	.	.	T	.	.	-0.14	0.01	.	*	F	1.15	1.20
	Gly	173	.	.	.	.	.	T	C	0.32	-0.10	.	*	F	2.20	1.96
	Pro	174	.	.	.	.	T	T	.	0.10	-0.36	.	.	F	2.50	0.97
	Thr	175	.	.	.	.	T	T	.	0.24	0.33	.	*	F	1.65	0.55
	Ser	176	.	.	.	.	T	T	.	-0.01	0.41	.	.	F	1.10	0.30
55	Gly	177	.	.	.	.	T	.	.	0.00	0.41	.	.	F	0.65	0.30
	Leu	178	.	.	.	.	.	.	C	-0.24	0.37	.	.	F	0.50	0.28
	Cys	179	.	.	.	.	.	T	C	-0.33	0.39	.	.	F	0.75	0.21
	Pro	180	.	.	.	.	.	T	C	-0.23	0.39	.	.	F	1.05	0.28
	Ser	181	.	.	.	.	.	T	C	0.07	0.39	.	.	F	1.35	0.53
60	Ala	182	.	.	.	.	.	T	C	0.41	-0.30	.	*	F	2.40	1.72
	Ser	183	.	.	.	.	.	T	C	1.22	-0.87	.	*	F	3.00	1.93
	Pro	184	.	.	.	.	.	T	C	1.89	-1.30	.	.	F	2.70	2.40
	Glu	185	A	.	.	.	.	T	.	1.76	-1.69	.	.	F	2.20	4.12

Glu	186	A	.	.	.	.	T	.	1.17	-1.76	.	.	F	1.90	3.04
Asp	187	A	.	.	.	.	T	.	1.37	-1.46	.	.	F	1.60	1.38
Glu	188	A	.	.	.	.	T	.	1.28	-1.46	.	.	.	1.15	1.02
Gly	189	A	.	.	.	.	T	.	1.10	-1.03	.	.	.	1.00	0.75
Ile	190	A	.	.	.	.	T	.	0.71	-0.60	.	.	.	1.00	0.58

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 231.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
18 May 1998	209878

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 209878

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209878

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 233.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
February 12, 1998	209626

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(If the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. 209626

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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FINLAND

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ATCC Deposit No.: 209626

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SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

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United States of America

Date of deposit	Accession Number
20 March 1998	209683

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer			Authorized officer		

ATCC Deposit No. 209683

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209683

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 233.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
25 February 1998	209641

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. 209641
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209641

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 234.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
09 July 1997	209141

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 209141
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209141

UNITED KINGDOM

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DENMARK

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SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 234.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
26 February 1997	97901

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. 97901
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97901

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 234.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
18 May 1998	209877

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

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ATCC Deposit No. 209877
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209877

UNITED KINGDOM

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DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 234.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
11 August 1999	PTA-499

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Revised Form PCT/RO/134 (January 2001) Pctro134ep.sollist

ATCC Deposit No. PTA-499

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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ATCC Deposit No.: PTA-499

UNITED KINGDOM

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DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 235.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
14 January 1998	209580

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
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Authorized officer	Authorized officer

ATCC Deposit No. 209580

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209580

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 237.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
22 May 1998	209889

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

ATCC Deposit No. 209889
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209889

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 232.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
15 May 1997	209044

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 209044

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209044

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 233.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
13 March 1997	97958

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 97958

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97958

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 233.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
07 March 1997	97923

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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ATCC Deposit No. 97923

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 97923

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description in Table 1 on page 234.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
15 May 1997	209047

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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Authorized officer	Authorized officer

ATCC Deposit No. 209047
CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209047

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:X.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

```
                .         .         .         .         .
  1 ATGGCGGCGG CGGGCCGGCT CCCGAGCTCC TGGGCCCTCT TCTCGCCGCT 50
    M  A  A   A  G  R  L   P  S  S   W  A  L   F  S  P  L

                .         .         .         .         .
 51 CCTCGCAGGG CTTGCACTAC TGGGAGTCGG GCCGGTCCCA GCGCGGGCGC 100
     L  A  G   L  A  L   L  G  V  G   P  V  P   A  R  A

                .         .         .         .         .
101 TGCACAACGT CACGGCCGAG CTCTTTGGGG CCGAGGCCTG GGGCACCCTT 150
    L  H  N   V  T  A  E   L  F  G   A  E  A   W  G  T  L

                .         .         .         .         .
151 GCGGCTTTCG GGGACCTCAA CTCCGACAAG CAGACGGATC TCTTCGTGCT 200
    A  A  F   G  D  L  N   S  D  K   Q  T  D   L  F  V  L

                .         .         .         .         .
201 GCGGGAAAGA AATGACTTAA TCGTCTTTTT GGCAGACCAG AATGCACCCT 250
     R  E  R   N  D  L   I  V  F  L   A  D  Q   N  A  P

                .         .         .         .         .
251 ATTTTAAACC CAAAGTAAAG GTATCTTTCA AGAATCACAG TGCATTGATA 300
    Y  F  K   P  K  V   K  V  S  F   K  N  H   S  A  L  I

                .         .         .         .         .
301 ACAAGTGTAG TCCCTGGGGA TTATGATGGA GATTCTCAAA TGGATGTCCT 350
    T  S  V   V  P  G   D  Y  D  G   D  S  Q   M  D  V  L

                .         .         .         .         .
351 TCTGACATAT CTTCCCAAAA ATTATGCCAA GAGTGAATTA GGAGCTGTTA 400
     L  T  Y   L  P  K   N  Y  A  K   S  E  L   G  A  V

                .         .         .         .         .
401 TCTTCTGGGG ACAAAATCAA ACATTAGATC CTAACAATAT GACCATACTC 450
    I  F  W   G  Q  N   Q  T  L  D   P  N  N   M  T  I  L

                .         .         .         .         .
451 AATAGGACTT TTCAAGATGA GCCACTAATT ATGGATTTCA ATGGTGATCT 500
    N  R  T   F  Q  D   E  P  L  I   M  D  F   N  G  D  L

                .         .         .         .         .
501 AATTCCTGAT ATTTTTGGTA TCACAAATGA ATCCAACCAG CCACAGATAC 550
     I  P  D   I  F  G   I  T  N  E   S  N  Q   P  Q  I

                .         .         .         .         .
551 TATTAGGAGG GAATTTATCA TGGCATCCAG CATTGACCAC TACAAGTAAA 600
    L  L  G   G  N  L   S  W  H  P   A  L  T   T  T  S  K

                .         .         .         .         .
```

Figure 1A

```
601 ATGCGAATTC CACATTCTCA TGCATTTATT GATCTGACTG AAGATTTTAC 650
    M  R  I  P  H  S  H  A  F  I  D  L  T  E  D  F  T

651 AGCAGATTTA TTCCTGACGA CATTGAATGC CACCACTAGT ACCTTCCAGT 700
    A  D  L  F  L  T  T  L  N  A  T  T  S  T  F  Q

701 TTGAAATATG GGAAAATTTG GATGGAAACT TCTCTGTCAG TACTATATTG 750
    F  E  I  W  E  N  L  D  G  N  F  S  V  S  T  I  L

751 GAAAAACCTC AAAATATGAT GGTGGTTGGA CAGTCAGCAT TTGCAGACTT 800
    E  K  P  Q  N  M  M  V  V  G  Q  S  A  F  A  D  F

801 TGATGGAGAT GGACACATGG ATCATTTACT GCCAGGCTGT GAAGATAAAA 850
    D  G  D  G  H  M  D  H  L  L  P  G  C  E  D  K

851 ATTGCCAAAA GAGTACCATC TACTTAGTGA GATCTGGGAT GAAGCAGTGG 900
    N  C  Q  K  S  T  I  Y  L  V  R  S  G  M  K  Q  W

901 GTTCCAGTCC TACAAGATTT CAGCAATAAG GGCACACTCT GGGGCTTTGT 950
    V  P  V  L  Q  D  F  S  N  K  G  T  L  W  G  F  V

951 GCCATTTGTG GATGAACAGC AACCAACTGA AATACCAATT CCAATTACCC 1000
    P  F  V  D  E  Q  Q  P  T  E  I  P  I  P  I  T

1001 TTCATATTGG AGACTACAAT ATGGATGGCT ATCCAGACGC TCTGGTCATA 1050
    L  H  I  G  D  Y  N  M  D  G  Y  P  D  A  L  V  I

1051 CTAAAGAACA CATCTGGAAG CAACCAGCAG GCCTTTTTAC TGGAGAACGT 1100
    L  K  N  T  S  G  S  N  Q  Q  A  F  L  L  E  N  V

1101 CCCTTGTAAT AATGCAAGCT GTGAAGAGGC GCGTCGAATG TTTAAAGTCT 1150
    P  C  N  N  A  S  C  E  E  A  R  R  M  F  K  V

1151 ACTGGGAGCT GACAGACCTA AATCAAATTA AGGATGCCAT GGTTGCCACC 1200
    Y  W  E  L  T  D  L  N  Q  I  K  D  A  M  V  A  T
```

Figure 1B

```
1201 TTCTTTGACA TTTACGAAGA TGGAATCTTG GACATTGTAG TGCTAAGTAA 1250
     F  F  D  I  Y  E  D  G  I  L  D  I  V  V  L  S  K
                .        .        .        .        .
1251 AGGATATACA AAGAATGATT TTGCCATTCA TACACTAAAA AATAACTTTG 1300
     G  Y  T  K  N  D  F  A  I  H  T  L  K  N  N  F
                .        .        .        .        .
1301 AAGCAGATGC TTATTTTGTT AAAGTTATTG TTCTTAGTGG TCTGTGTTCT 1350
     E  A  D  A  Y  F  V  K  V  I  V  L  S  G  L  C  S
                .        .        .        .        .
1351 AATGACTGTC CTCGTAAGAT AACACCCTTT GGAGTGAATC AACCTGGACC 1400
     N  D  C  P  R  K  I  T  P  F  G  V  N  Q  P  G  P
                .        .        .        .        .
1401 TTATATCATG TATACAACTG TAGATGCAAA TGGGTATCTG AAAAATGGAT 1450
     Y  I  M  Y  T  T  V  D  A  N  G  Y  L  K  N  G
                .        .        .        .        .
1451 CAGCTGGCCA ACTCAGCCAA TCCGCACATT TAGCTCTCCA ACTACCATAC 1500
     S  A  G  Q  L  S  Q  S  A  H  L  A  L  Q  L  P  Y
                .        .        .        .        .
1501 AACGTGCTTG GTTTAGGTCG GAGCGCAAAT TTTCTTGACC ATCTCTACGT 1550
     N  V  L  G  L  G  R  S  A  N  F  L  D  H  L  Y  V
                .        .        .        .        .
1551 TGGTATTCCC CGTCCATCTG GAGAAAAATC TATACGAAAA CAAGAGTGGA 1600
     G  I  P  R  P  S  G  E  K  S  I  R  K  Q  E  W
                .        .        .        .        .
1601 CTGCAATCAT TCCAAATTCC CAGCTAATTG TCATTCCATA CCCTCACAAT 1650
     T  A  I  I  P  N  S  Q  L  I  V  I  P  Y  P  H  N
                .        .        .        .        .
1651 GTCCCTCGAA GTTGGAGTGC CAAACTGTAT CTTACACCAA GTAATATTGT 1700
     V  P  R  S  W  S  A  K  L  Y  L  T  P  S  N  I  V
                .        .        .        .        .
1701 TCTGCTTACT GCTATAGCTC TCATCGGTGT CTGTGTTTTC ATCTTGGCAA 1750
     L  L  T  A  I  A  L  I  G  V  C  V  F  I  L  A
                .        .        .        .        .
1751 TAATTGGCAT TTTACATTGG CAGGAAAAGA AAGCAGATGA TAGAGAAAAA 1800
     I  I  G  I  L  H  W  Q  E  K  K  A  D  D  R  E  K
                .        .        .
1801 CGACAAGAAG CCCACCGGTT TCATTTTGAT GCTATGTGA 1839
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```

Figure 1C

Figure 2

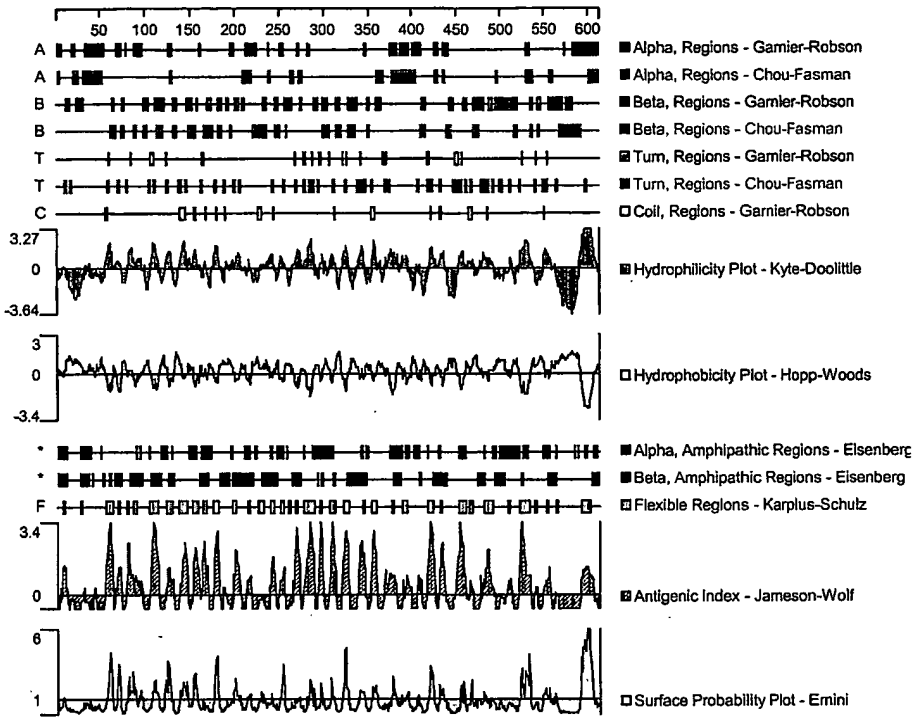

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A
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B
T
T
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Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
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Hydrophobicity Plot - Hopp-Woods
*
*
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Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
Surface Probability Plot - Emini

Figure 3A

```
   1  GGTCGACGGTATCGATAAGCTTGATATCGAATTCCTGCAACAGTTCTTGGAAACCCACTC   60

  61  GAGAGGGCCACGCCTCCATTCACCAGGCCACGCATCACAAGAGGCAACACCAGGAGCCAA  120

 121  CATGAGCTCGGGGACTGAACTGCTGTGGCCCGGAGCAGCGCTGCTGGTGCTGTTGGGGGT  180
   1   M  S  S  G  T  E  L  L  W  P  G  A  A  L  L  V  L  L  G  V   20

 181  GGCAGCCAGTCTGTGTGTGCGCTGCTCACGCCCAGGTGCAAAGAGGTCAGAGAAAATCTA  240
  21   A  A  S  L  C  V  R  C  S  R  P  G  A  K  R  S  E  K  I  Y   40

 241  CCAGCAGAGAAGTCTGCGTGAGGACCAACAGAGCTTTACGGGGTCCCGGACCTACTCCTT  300
  41   Q  Q  R  S  L  R  E  D  Q  Q  S  F  T  G  S  R  T  Y  S  L   60

 301  GGTCGGGCAGGCATGGCCAGGACCCCTGGCGGACATGGCACCCACAAGGAAGGACAAGCT  360
  61   V  G  Q  A  W  P  G  P  L  A  D  M  A  P  T  R  K  D  K  L   80

 361  GTTGCAATTCTACCCCAGCCTGGAGGATCCAGCATCTTCCAGGTACCAGAACTTCAGCAA  420
  81   L  Q  F  Y  P  S  L  E  D  P  A  S  S  R  Y  Q  N  F  S  K  100

 421  AGGAAGCAGACACGGGTCGGAGGAAGCCTACATAGACCCCATTGCCATGGAGTATTACAA  480
 101   G  S  R  H  G  S  E  E  A  Y  I  D  P  I  A  M  E  Y  Y  N  120

 481  CTGGGGGCGGTTCTCGAAGCCCCCAGAAGATGATGATGCCAATTCCTACGAGAATGTGCT  540
 121   W  G  R  F  S  K  P  P  E  D  D  D  A  N  S  Y  E  N  V  L  140

 541  CATTTGCAAGCAGAAAACCACAGAGACAGGTGCCCAGCAGGAGGGCATAGGTGGCCTCTG  600
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 601  CAGAGGGGACCTCAGCCTGTCACTGGCCCTGAAGACTGGCCCCACTTCTGGTCTCTGTCC  660
 161   R  G  D  L  S  L  S  L  A  L  K  T  G  P  T  S  G  L  C  P  180

 661  CTCTGCCTCCCCGGAAGAAGATGAAGGAATCTGAGGATTATCAGAACTTCAGCATTCCAT  720
 181   S  A  S  P  E  E  D  E  G  I  *                             191

 721  CCATTCAGTGGCGCGAGTCCAGGAAGGTCATGGGGCAACTCCAGAGAAGAAAGCATCCCC  780

 781  TGGCCCGGTGGGAAGCCCAGACGAGGAGGACGGGGAACCGGATTACGTGAATGGGGAGGT  840

 841  GGCAGCCACAGAAGCCTAGGGCAGACCAAGAAGAAAGGAGCCAAGGCAAAGAGGGACCAC  900
```

Figure 3B

```
 901  TGTGCTCATGGACCCATCGCTGCCTTCCAAGGACCATTTCCCAGAGCTACTCAACTTTTA   960

 961  AGCCCCTGCCATGGTTGCTCCTGGAAGGAGAACCAGCCACCCTGAGGACCACCTGGCCAT  1020

1021  GCGTGCACAGCCTGGGAAAAGACAGTTACTCACGGGAGCTGCAGGCCCCGTCACCAAGCC  1080

1081  CTCTCCCGACCCAGGCTTTGTGGGGCAGGCACCTGGTACCAAGGGTAACCCGGCTCCTGG  1140

1141  TATGGACGGATGCGCAGGATTTAGGATAAGCTGTCACCCAGTCCCCATAACAAAACCACT  1200

1201  GTCCAACACTGGTATCTGTGTTCTTTTGTGCTATGAATTTGGATTCCTAATTGCTATTGT  1260

1261  TGGTTGCTGGGGTTTTAAATGATTGATAAGCTTGTACAGTTAACTTATAGAGGGGGAGCC  1320

1321  ATATTTAACATTCTGGATTTCAGAGTAGAGATTTCTGTGTTGTCTCCTAGAAAGCATTAC  1380

1381  ATGTAGTTTATTTCAGCATCCTTGTTGGGTGGGGCCCTGGCTCTCTTCCCCTTTGGTGGG  1440

1441  ACCTCCCCTTTCTTTGGGCTTCAGTTCACTCAGGAAGAAATGAGGCTGTCGCCATCTTTA  1500

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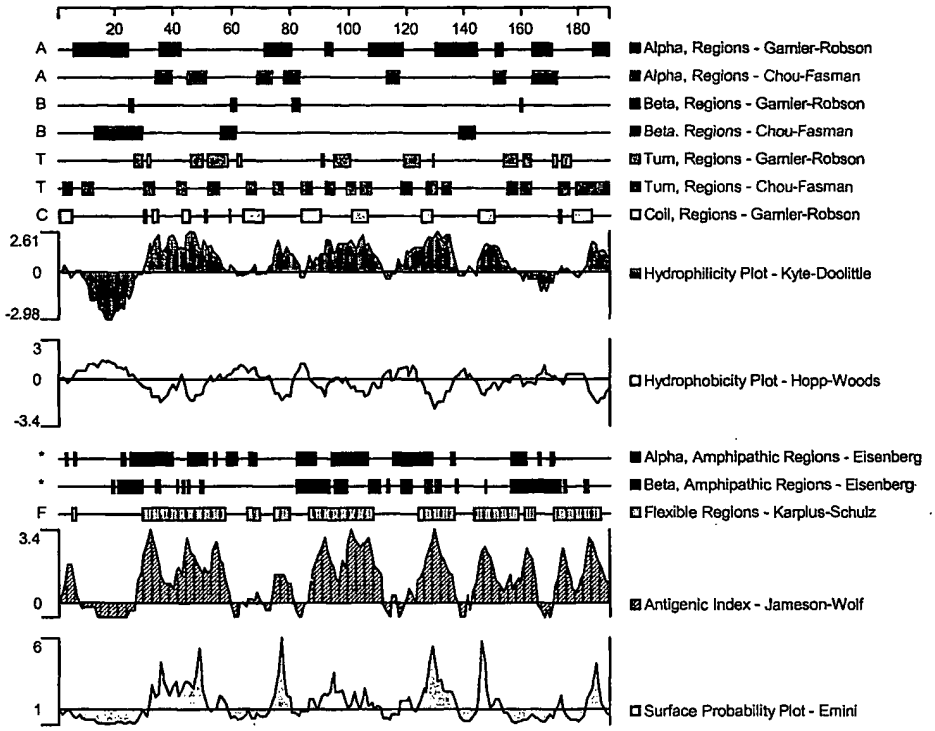
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1681  CCCAGAGGGACCTTGAGTCAGAAATGTTGCCAGAAAAAGTATCTCCTCCAACCAAAACAT  1740

1741  CTCAATAAAACCATTTTAGTTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  1797
```

Figure 4


20
40
60
80
100
120
140
160
180
A
A
B
B
T
T
C
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
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Turn, Regions - Garnier-Robson
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Beta, Amphipathic Regions - Eisenberg
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Surface Probability Plot - Emini

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<210> 3
<211> 86
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic sequence with 4 tandem copies of the GAS binding site found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)), 18 nucleotides complementary to the SV40 early promoter, and a Xho I restriction site.

<400> 3
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60
cccgaaatat ctgccatctc aattag 86

<210> 4
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic sequence complementary to the SV40 promter; includes a Hind III restriction site.

<400> 4
gcggcaagct ttttgcaaag cctaggc 27

<210> 5
<211> 271
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes GAS binding sites found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)).

<400> 5
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60
aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc 120
gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat 180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240
ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 6
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence (Sakamoto et al., Oncogene 6:867-871 (1991)); includes a Xho I restriction site.

<400> 6
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 7
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence (Sakamoto et al., Oncogene 6:867-871 (1991)); includes a Hind III restriction site.

<400> 7
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 8
<211> 12
<212> DNA
<213> Homo sapiens

<400> 8
ggggactttc cc 12

<210> 9
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<221> Primer_Bind
<223> Synthetic primer with 4 tandem copies of the NF-KB binding site (GGGGACTTTCCC), 18 nucleotides complementary to the 5' end of the SV40 early promoter sequence, and a XhoI restriction site.

<400> 9
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg 60
ccatctcaat tag 73

<210> 10
<211> 256
<212> DNA
<213> Artificial Sequence

<220>
<221> Protein_Bind
<223> Synthetic promoter for use in biological assays; includes NF-KB binding sites.

<400> 10
ctcgagggga ctttcccggg gactttccgg ggactttccg ggactttcca tctgccatct 60
caattagtca gcaaccatag tcccgccccc aactccgccc atcccgcccc taactccgcc 120

cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga 180
ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggctttttg gaggcctagg 240
cttttgcaaa aagctt 256

<210> 11
<211> 1113
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (393)..(393)
<223> n equals a,t,g, or c

<400> 11
gatgctcctt tagcttggag gagtttgtta ttacccacct tctgaagcct acttctgtca 60
attcatccaa ctcattctca gtccagtttt gtttccttgc tggtgaggag ttgtgatcct 120
ttggaggaga agaggcattc tggtttttgg aatttttagc cattttgctc tggtttcttc 180
ccatctttgt ggatttatct acctttcatc ttcaatgtta gtgacctatg gatggggtct 240
ctgagtggat gtgctcttcc tttctgtttg twagttttct ttctaacagt tagcccctct 300
gctgtaggtc tgctggaktt tgctggaggt ccactccaga ccctgtttgc ctgggtatca 360
ccagtggagg ctgcagaaca gcaaagattg ctncctgttc tttcctctgg aagcttcgtc 420
tcagagggca cctgccagat gccagccaga gctctcctgt atgaggtgtc tgttggccca 480
tactgggaga ttcctcccag tcaggataca aggaggtcag ggacctactt gaggaggcag 540
tctgaccctt agcagaggtt gaacactgtg ctaggaggtc ctctgctctt ttcagagctg 600
tcaggcgggg cgtataagtc tgctgaatct gtgtccgcag ccaccccttc ccccaggtgc 660
tctgtcccag ggagatgggg gttttatttt taagtcccca actggggctg ctgccttttt 720
ttcagagatg ccctgcccag agaggagaaa tctggcagtc tggcctcaga ggccttgctg 780
agctgccgtt ggctccaccc agttcaaact tcccaagggg ctttgtttat actgtaaggg 840
gaaaaccgcc tactcgagcc tcatcaatgg cagacacccc tccccgcgcc aagcttaagt 900
gtcccaggtt gatctcagac tgctgctgtg ctggcagtga gaatttcaag ccagtggatc 960
ttagtttgct gtgctctgtg ggggtgggac ccattgaacc agactactcg gctccctggc 1020
ttcagccccc tttccaggag agtgaagggt tctgtctcat tggcattcca ggagtcactg 1080
gtgtatggaa aaaaaaaaaa aaagggcggc cgc 1113

<210> 12
<211> 983
<212> DNA
<213> Homo sapiens

<400> 12
ggcacgaggg cagctgcaga gctccaggtt tctctgccca caagggcagg ggctgccccc 60
cgcccaggat gactctgcct tccagagcct tggcctccct gggggtggga gtgtgggga 120
tgctaaggtt aaatcaggtc acagtaagtt gtgggggcag caggtggagc agcagagtgg 180
cactgggagc tttctcttgg gtgtgcggtg tggccttggt tctgcagcca tcaggtgggg 240
gcttgggact gacttctcct tctgaaggat gctgggaagg tgagctggct ttggcagtgc 300
ttagagctcc ggggggttcc ccctcctaga acatgcaagc tctcacaccg gtgcgtcatc 360
atcacaccca tcatcaagcc cacagtggta tactgaacac ctgccccaca aagacggtgg 420
actgctctca gaggagcccc atgaaccacc gatggttaca actatccaat gcctgatggc 480
agacagccag gccaacctcg gcttccactc tctcttcctc accctacaat cagccaaagt 540
gacctgagtc atgtagtgtg aagttgcttt ctgctttctc ttgtttgtgc ttttgctgtt 600
tcttctgccc catactttgt taactccatg agttaaatgc tacccatttt cccagacaag 660
tgctgcttct gcaaggaaac ccttcctgat cccccaccta tctgaaaagt acctctccag 720
cttgcttctt cagggtgctg agcgttcctt cccagcctgt catcaccttc ctccatacgc 780
tatggtgtgt tcctgtcttc tctagtcttg tcctcttttt tctgttagat tgtagctcct 840
tgctgacagg aaccacgcct gctccagctt catacctccc actgctacag cacagaacct 900
gcttctcaga cttacagcaa atgtttgttt gctgaatgaa ttaattaaag ataaagcaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 13

<211> 973
<212> DNA
<213> Homo sapiens

<400> 13
ggcacgagcc cagcggaagc caagccacca ggccccccag cgtccacgcg gagcatgaac 60
attgaggatg gcgcgtgccc gcggctcccc gtgccccccg ctgccgcccg gtaggatgtc 120
ctggccccac ggggcattgc tcttcctctg gctcttctcc ccacccctgg gggccggtgg 180
aggtggagtg gccgtgacgt ctgccgccgg agggggctcc ccgccggcca cctcctgccc 240
cgtggcctgc tcctgcagca accaggccag ccgggtgatc tgcacacgga gagacctggc 300
cgaggtccca gccagcatcc cggtcaacac gcggtacctg aacctgcaag agaacggcat 360
ccaggtgatc cggacggaca cgttcaagca cctgcggcac ctggagattc tgcagctgag 420
caagaacctg gtgcgcaaga tcgaggtggg cgccttcaac gggctgccca gcctcaacac 480
gctggagctt tttgacaacc ggctgaccac ggtgcccacg caggccttcg agtacctgtc 540
caagctgcgg gagctctggc tgcggaacaa ccccatcgag agcatcccct cctacgcctt 600
caaccgcgtg ccctcgctgc ggcgcctgga cctgggcgag ctcaagcggc tggaatacat 660
ctcggaggcg gccttcgagg ggctggtcaa cctgcgctac ctcaacctgg gcatgtgcaa 720
cctcaaggac atccccaacc tgacggccct ggtgcgcctg gaggagctgg agctgtcggg 780
caaccggctg gacctgatcc gcccgggctc cttccagggt ctcaccagcc tgcgcaagct 840
gtggctcatg cacgcccagg tagccaccat cgagcgcaac gccttcgacg acctcaagtc 900
gctggaggag ctcaacctgt cccacaacaa cctgatgtcg ctgccccacg acctcttcac 960
gcccctgcac cgc 973

<210> 14
<211> 1458
<212> DNA
<213> Homo sapiens

<400> 14
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caacagaagc ggtgatcgtc taagtatgag cctgtggctt cctttgtgca tttgagcatg 120
ctgtaattaa gatgagatca gtttcttaga aaaagctttc ctgaatccct ctgacgttgc 180
ctgggatctt tctgttgatt cgtcttttct ggagattggg acagagcatc tgtggtccag 240
ggaagttagt cctctggcct caattctgtt gtggatgtgc agtgataagc gggcattgcg 300
tgcctcgggg gatgcctagt tcgtggcttc ctggctgttt tgtccttctg tgtcttgtag 360
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ctttgccgca cctccaggtt ctgggcatga gaggccgtgg cctcatttct ggtggataac 480
ctttttagtt taatagcatc tttaattaga tcacagcatt gaattcaaaa tttcttctgc 540
aaagaaagtt gtggggcata agacaccggg aatgagggag gaggaagaca gttgtgtttt 600
ctctttaaac cttgagctct agccgatgca tttgtcagga aatacagcac tttgtcttaa 660
gaaaacaagg aaggaggccg ggcgcagtgg ctcacgcctg taatcccagc actttgggag 720
gccgaggcgg gcggatcacc tgaggtgggg agtatgagac caccctgact aacatggaga 780
gaccctgtct ctactaaaag tacagaatta gccgggcgtg gttgcgcatg cccataatcc 840
cagctactga ggagacttga ggtaggagaa tcacttgaac ctcagcggcg gaggttgcag 900
tgagtcgaga tcgcgccagt gcactccagc ctgggcaaga agagcgaaac tgggtctcaa 960
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tataaatatg catatacagt gtatgtataa agcagaatgc ctgcctttcc tggttatttt 1260
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aaatgttttt attgtgcata aatacatact aatgttgatc taaaaaaaaa aaaaaaaaaa 1440
aaaaaaaaaa aaaaaaaa 1458

<210> 15
<211> 2005
<212> DNA
<213> Homo sapiens

<400> 15
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gcgctgcctg cccgaggcgg ttcacgtaaa gacagcgaga tcctgagggc cagccgggaa 120
ggaggcgtgg atatggagct ggctgctgcc aagtccgggg cccgcgccgc tgcctagcgc 180
gtcctgggga ctctgtgggg acgcgccccg cgccgcggct cggggacccg tagagcccgg 240
cgctgcgcgc atggccctgc tctcgcgccc cgcgctcacc ctcctgctcc tcctcatggc 300
cgctgttgtc aggtgccagg agcaggccca gaccaccgac tggagagcca ccctgaagac 360
catccggaac ggcgttcata agatagacac gtacctgaac gccgccttgg acctcctggg 420
aggcgaggac ggtctctgcc agtataaatg cagtgacgga tctaagcctt tcccacgtta 480
tggttataaa ccctccccac cgaatggatg tggctctcca ctgtttggtg ktcatcttaa 540
cattggtatc ccttccctga caaagtgttg caaccaacac gacaggtgct atgaracctg 600
tggcaaaagc aagaatgact gtgatgaaga attccagtat tgcctctcca agatctgccg 660
agatgtacag aaaacactag gactaactca gcatgttcag gcatgtgaaa caacagtgga 720
gctcttgttt gacagtgtta tacatttagg ttgtaaacca tatctggaca gccaacgagc 780
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gacagatgaa gatggaagaa cataaccttt gacaaataac taatgttttt acaacataaa 900
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tagagccaaa aggatggaaa aggcaagata taaatgcctt ttatagatct cttatttaca 1860
ttgaaaatta ttaccatatg tttagagcaa atccaagaaa acttcaacag cttctgaaga 1920
tgtctatgaa tgttgaaaac ttttcaatst cttggratgc tcakttaatt cgcagaccgg 1980
cttaacggat taaacgcccc ccccc 2005

<210> 16
<211> 943
<212> DNA
<213> Homo sapiens

<400> 16
ggcacgagct ccgcccggcc ccgaggggct ctccccggag gctcagcccc ctctgctccc 60
catgggcaac tgccaggcag ggcacaacct gcacctgtgt ctggcccacc acccacctct 120
ggtctgtgcc actttgatcc tgctgctcct tggcctctct ggcctgggcc ttggcagctt 180
cctcctcacc cacaggactg gcctgcgcac cctgacatcc cccaggactg ggtctctttt 240
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aacaagaccc ggacattcca ggccacagtc ctgggaagtc agatgggatt gaaaggatct 420
tctgcaggac aactggtcct tatcacagcc agggtgacca cagaaaggac tgcaggaacc 480
tgcctatatt ttagtgctgt tccaggaatc ctaccctcca gccagccacc catatcctgc 540
tcagaggagg gggctggaaa tgccaccctg agccctagaa tgggtgagga atgtgttagt 600
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tgtggctcca ggctgctggt cttgggctcc ttcctgcttc tcttctgtgg ccttctctgc 720
tgtgtcactg ctatgtgctt ccacccgcgc cgggagtccc actggtctag aacccggctc 780
tgagggcact ggcctagttc ccgacttgtt tctcaggtgt gaatcaactt cttgggcctt 840
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aagctttttt gcccaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 943

<210> 17

<211> 1503
<212> DNA
<213> Homo sapiens

<400> 17
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tgcctgtagc aggagccctg aggaggagga ggaagaggat gtgctgaaat acgtccggga 660
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tga 1503

<210> 18
<211> 1512
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (207)..(207)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (209)..(209)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (521)..(521)
<223> n equals a,t,g, or c

<400> 18
gcagagcccc tgggtgtgag aagctcgtct cccgtgggtt gcattggctc tgccctatct 60
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ttggacacag attggcaacc tgcctcaccm ckcccccctw cgctggggct tccatcttaa 1440
tttattctca ataataaaga cttcatgatg amaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500
aaaaaaaaaa aa 1512

<210> 19
<211> 1655
<212> DNA
<213> Homo sapiens

<400> 19
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taggttctgc tggtcacaca accctcggga tcacacttat gattgggggt ataacgtgta 180
ttctttcact aatctgtgcc ttggctcttg cctacttgga tcagagagca gagagaatcc 240
ttcataaaga acaaggaaaa acaggtgaag ttattaaatt aactgatgta aaggacttct 300
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<210> 20
<211> 2525
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (5)..(5)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (10)..(10)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1354)..(1354)
<223> n equals a,t,g, or c

<400> 20
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cagtggaatg gaaaaacagt gctgtagtca tcctgtaata tgctccttgt caacaatgta 180
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gccgc 2525

<210> 21
<211> 1396
<212> DNA
<213> Homo sapiens

<400> 21
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agctgctgtt tgaattatct gtgaatgttg ggaagaggaa tgccagagct gccggctgaa 180
aattacccaa ccaagagaaa tctgcaggat ggactttctg gtcctcttct tgttctacct 240
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<210> 22
<211> 1069
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (508)..(508)
<223> n equals a,t,g, or c

<400> 22
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atggctgacc cccatgtctc atttctaagc ttcaggcagc ttttctcctg ggcagctgtc 240
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ctggcagtct acccccttca tctccccgtg gaggctccat gcctagaggt ggtcttcaaa 360
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<210> 23
<211> 1658
<212> DNA
<213> Homo sapiens

<400> 23
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tgccttctgg atgccctcat cctcctcggg gctggggtct ccctcaaggc cacccagctc 180
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cccctgatct gcctctgcac acctcatcgc ttcaaaaa 1658

<210> 24
<211> 1077
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1036)..(1036)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1038)..(1038)
<223> n equals a,t,g, or c

<400> 24
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gcttctccta aatctccgtt ctctgggtaa ggggagtcca agcctctgtc atgaggaacg 300
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gcgattcctg cagcggaaga ggcgtgatct ggccttcgac tcgctatgtc cactaacaat 420
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<210> 25
<211> 1205
<212> DNA
<213> Homo sapiens

<400> 25
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ccttgtgggt gggggacagc aaatgaggga cctctctttt ctctacactc tcctttggct 180
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aaaaa 1205

<210> 26
<211> 1674
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1663)..(1663)
<223> n equals a,t,g, or c

<400> 26
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<210> 27
<211> 1965
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (333)..(333)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1961)..(1961)
<223> n equals a,t,g, or c

<400> 27
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<211> 1863
<212> DNA
<213> Homo sapiens

<400> 28
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<211> 1626
<212> DNA
<213> Homo sapiens

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aaaaaa 1626

<210> 30
<211> 605
<212> DNA
<213> Homo sapiens

<400> 30
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aaaaa 605

<210> 31
<211> 931
<212> DNA
<213> Homo sapiens

<400> 31
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<210> 32
<211> 1407
<212> DNA
<213> Homo sapiens

<400> 32
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<210> 33
<211> 1526
<212> DNA
<213> Homo sapiens

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<210> 34
<211> 1737
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<222> (1674)..(1674)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1731)..(1731)
<223> n equals a,t,g, or c

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<210> 35
<211> 2312
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<222> (2312)..(2312)
<223> n equals a,t,g, or c

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aaaaaaaaaa aaaaaaaaaa aaaacaaaaa an 2312

<210> 36
<211> 2235
<212> DNA
<213> Homo sapiens

<400> 36
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<211> 2971
<212> DNA
<213> Homo sapiens

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<211> 1163
<212> DNA
<213> Homo sapiens

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<210> 39
<211> 1932
<212> DNA
<213> Homo sapiens

<220>

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<223> n equals a,t,g, or c

<400> 39
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<210> 40
<211> 881
<212> DNA
<213> Homo sapiens

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<210> 41
<211> 1932
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2)..(2)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1022)..(1022)
<223> n equals a,t,g, or c

<400> 41
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<210> 42
<211> 1164
<212> DNA
<213> Homo sapiens

<220>
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<222> (582)..(582)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (592)..(592)
<223> n equals a,t,g, or c

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<210> 43
<211> 1105
<212> DNA
<213> Homo sapiens

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<211> 703
<212> DNA
<213> Homo sapiens

<400> 48
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<210> 49
<211> 639
<212> DNA
<213> Homo sapiens

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<211> 867
<212> DNA

<213> Homo sapiens

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<212> DNA
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<223> n equals a,t,g, or c

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<211> 1196

<212> DNA
<213> Homo sapiens

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<222> (590)..(590)
<223> n equals a,t,g, or c

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<210> 53
<211> 945
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (295)..(295)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (875)..(875)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (914)..(914)
<223> n equals a,t,g, or c

<400> 53
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aagaaataaa atatcaaacg attggaaaga tgttaatgtg tcatcattca tagaaaacat 180
gattcataga tatacataca cgaatgcttt gaattcataa gtagattcag ccagttgctg 240
gatataaagt caatatacaa aaactatttt tatagacatg aaacacgcaa tgagnaaaaa 300
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atagccctga acatttgtaa tatatgactt ttggtgaatg tagcattcat ttctgttgat 480

tacaaactca ggggtgaaat tgttgagtcc taagggagct atagatgtat tcaacttcag 540
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<210> 54
<211> 488
<212> DNA
<213> Homo sapiens

<400> 54
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catgggagac ctcaaggagg tatgcctgcc ccacagatgc cctggaagga cagcttgctg 180
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gatgtggagg gagaacagct caagaccacg gaacagcctg ctctcccgct tcctggcttc 360
cgtgcgcttt tgtccaatca ggctttttga ccaatcggcc aggcgcgcta tgtaaatttc 420
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aaaaaaaa 488

<210> 55
<211> 2860
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (753)..(753)
<223> n equals a,t,g, or c

<400> 55
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gggcaccagg tcttgctgct cctgcttctc acctctgcag tggcagcagg cccctggccc 240
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acttaagtgt aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2860

<210> 56
<211> 1559
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1445)..(1445)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1551)..(1551)
<223> n equals a,t,g, or c

<400> 56
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cgacctgaac tgtcaaaaaa aaaaaaaaaa aaacccgrgg gggggcccgg nacccaatt 1559

<210> 57
<211> 2064
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2001)..(2001)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2024)..(2024)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (2049)..(2049)
<223> n equals a,t,g, or c

<400> 57
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tccccaacng ggaccagggg ggtc 2064

<210> 58
<211> 1050
<212> DNA
<213> Homo sapiens

<400> 58
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ctacccccctg gccccacaat aaacatgatc tgaagcagca aaaaaaaaaa aaaaaaaaaa 1020
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1050

<210> 59
<211> 2533
<212> DNA
<213> Homo sapiens

<400> 59
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<210> 60
<211> 899
<212> DNA
<213> Homo sapiens

<400> 60
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<211> 1079
<212> DNA
<213> Homo sapiens

<400> 61
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<210> 62
<211> 1928
<212> DNA
<213> Homo sapiens

<400> 62
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aaaaaaaa 1928

<210> 63
<211> 781
<212> DNA
<213> Homo sapiens

<400> 63
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tcttcagaga tgccctgccc caagacgggg actctagaga ggcagtctgg ctgcagtggc 660
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<210> 64
<211> 1194
<212> DNA
<213> Homo sapiens

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<222> (1172)..(1172)
<223> n equals a,t,g, or c

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<210> 65
<211> 1677
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1012)..(1012)
<223> n equals a,t,g, or c

<400> 65
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tctggctgta gtgggaggga gcagaggagt gaatgattgt cagttgggag ggtgcagagt 360
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<210> 66
<211> 1237
<212> DNA
<213> Homo sapiens

<400> 66
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<210> 67
<211> 1934
<212> DNA
<213> Homo sapiens

<400> 67
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<210> 68
<211> 3300
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

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<221> misc_feature
<222> (3)..(3)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (15)..(15)
<223> n equals a,t,g, or c

<400> 68
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<213> Homo sapiens

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<211> 1373
<212> DNA
<213> Homo sapiens

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<211> 1579
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<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 2703
<212> DNA
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<210> 76
<211> 742
<212> DNA
<213> Homo sapiens

<220>
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<222> (707)..(707)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (724)..(724)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (726)..(726)
<223> n equals a,t,g, or c

<400> 76
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ttggagggca cttctttcgt ggtagttctt ttatttttat taatctctgt atccttagat 180
agtcctccaa caaccaaagg ttgggactct gtcttacata tctgggtgcc cctcatagtg 240
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ttaactattt taaagtgaga agttcagtgc cacttagtat tgttaacaat gttgcataac 420
caccaccttt atttaaagtt ccaaaaaaaa tgttctcctc taaaaggaaa ccccatccca 480
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<210> 77
<211> 1825
<212> DNA
<213> Homo sapiens

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aaagaaagaa gataaaaaaa aaaaa 1825

<210> 78
<211> 1674
<212> DNA
<213> Homo sapiens

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<210> 79
<211> 2191
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1327)..(1327)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1334)..(1334)
<223> n equals a,t,g, or c

<400> 79
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<210> 80
<211> 1335
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1287)..(1287)
<223> n equals a,t,g, or c

<400> 80
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aaaaaaaaaa aaaaa 1335

<210> 81
<211> 1867
<212> DNA
<213> Homo sapiens

<400> 81
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caccctccag tccaaggcca gttatctctc caaaacacga cccacacgag gacctcgcat 1800
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aaaaaaa 1867

<210> 82
<211> 984
<212> DNA

<213> Homo sapiens

<400> 82
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<210> 83
<211> 2664
<212> DNA
<213> Homo sapiens

<400> 83
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<211> 1328
<212> DNA
<213> Homo sapiens

<400> 84
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<210> 85
<211> 1342
<212> DNA
<213> Homo sapiens

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acatgtggat cctcgttttc ca 1342

<210> 86
<211> 1154
<212> DNA
<213> Homo sapiens

<400> 86
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gaaactctgg ggtgaggcct ggttatctgc tgtaacagac cttccagtgg gttctgatgc 180
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<210> 87
<211> 1197
<212> DNA
<213> Homo sapiens

<220>
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<222> (573)..(573)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1177)..(1177)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1185)..(1185)
<223> n equals a,t,g, or c

<400> 87
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<210> 88
<211> 910
<212> DNA
<213> Homo sapiens

<400> 88
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<210> 89
<211> 1076
<212> DNA
<213> Homo sapiens

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<221> misc_feature
<222> (1029)..(1029)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1037)..(1037)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1040)..(1040)
<223> n equals a,t,g, or c

<400> 89
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<210> 90
<211> 1842
<212> DNA
<213> Homo sapiens

<220>
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<222> (67)..(67)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (98)..(98)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (212)..(212)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1838)..(1838)
<223> n equals a,t,g, or c

<400> 90
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<210> 91
<211> 1963
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (335)..(335)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1959)..(1959)
<223> n equals a,t,g, or c

<400> 91
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<210> 92
<211> 1487
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1470)..(1470)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1487)..(1487)
<223> n equals a,t,g, or c

<400> 92
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<210> 93
<211> 1653
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (67)..(67)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (212)..(212)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1636)..(1636)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (1653)..(1653)
<223> n equals a,t,g, or c

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aaaaaaaaaa aaaaancccg ggggggggcc ccn 1653

<210> 94
<211> 1830
<212> DNA
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (97)..(97)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (211)..(211)

<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<211> 1134
<212> DNA
<213> Homo sapiens

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<210> 96
<211> 1772
<212> DNA
<213> Homo sapiens

<400> 96
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<210> 97
<211> 2242
<212> DNA
<213> Homo sapiens

<400> 97
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<210> 98
<211> 2381
<212> DNA
<213> Homo sapiens

<400> 98
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<213> Homo sapiens

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<213> Homo sapiens

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35 40 45

Glu Gln Gln Arg Leu Leu Pro Val Leu Ser Ser Gly Ser Phe Val Ser
50 55 60

Glu Gly Thr Cys Gln Met Pro Ala Arg Ala Leu Leu Tyr Glu Val Ser
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Val Gly Pro Tyr Trp Glu Ile Pro Pro Ser Gln Asp Thr Arg Arg Ser
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Gly Thr Tyr Leu Arg Arg Gln Ser Asp Pro
100 105

<210> 105
<211> 86
<212> PRT
<213> Homo sapiens

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Pro Gly Gly Ser Pro Ser
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<213> Homo sapiens

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Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
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Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
     50                  55                  60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
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Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
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Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
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Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
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Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
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Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
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Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
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Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
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Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
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Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
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Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
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Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
        275                 280                 285

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg
    290                 295                 300
```

<210> 107
<211> 55
<212> PRT
<213> Homo sapiens

<400> 107

```
Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu Val
  1               5                  10                  15

Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser Ala
             20                  25                  30

Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg Gly
         35                  40                  45

Arg Gly Leu Ile Ser Gly Gly
     50                  55
```

<210> 108
<211> 189
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (94)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 108

```
Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Leu Met
  1               5                  10                  15

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
             20                  25                  30

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
         35                  40                  45

Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
     50                  55                  60
```

```
Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
 65                  70                  75                  80

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
                 85                  90                  95

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
            100                 105                 110

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
        115                 120                 125

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
    130                 135                 140

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
145                 150                 155                 160

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
                165                 170                 175

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
            180                 185
```

<210> 109
<211> 60
<212> PRT
<213> Homo sapiens

<400> 109

```
Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu Cys Leu Ala His
  1               5                  10                  15

His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu Leu Leu Gly Leu
             20                  25                  30

Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His Arg Thr Gly Leu
         35                  40                  45

Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe
     50                  55                  60
```

<210> 110
<211> 128
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (90)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 110
Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
1 5 10 15

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
20 25 30

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
35 40 45

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
50 55 60

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
65 70 75 80

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
85 90 95

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
100 105 110

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
115 120 125

<210> 111
<211> 68
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 111
Met Pro His Phe Leu Asp Trp Phe Val Pro Val Tyr Leu Val Ile Ser
1 5 10 15

Val Leu Ile Leu Val Gly Phe Gly Ala Cys Ile Tyr Tyr Phe Glu Pro
20 25 30

Gly Leu Gln Glu Ala His Lys Trp Arg Met Gln Arg Pro Leu Val Asp
35 40 45

Arg Xaa Leu Arg Lys Thr Leu Met Val Arg Asp Asn Leu Ala Phe Gly
50 55 60

Gly Pro Glu Val
65

<210> 112

<211> 122
<212> PRT
<213> Homo sapiens

<400> 112
Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile Cys Ala Leu Ala
1 5 10 15

Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu His Lys Glu Gln
20 25 30

Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val Lys Asp Phe Ser
35 40 45

Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys Tyr Tyr Val Ala
50 55 60

Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe Thr Glu Lys Phe
65 70 75 80

Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser Val Val Tyr Val
85 90 95

Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu Val Asp Lys Thr
100 105 110

Gly Lys Asn Ile Ile Trp Val Leu Cys Ala
115 120

<210> 113
<211> 82
<212> PRT
<213> Homo sapiens

<400> 113
Met Glu Lys Gln Cys Cys Ser His Pro Val Ile Cys Ser Leu Ser Thr
1 5 10 15

Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Ser
20 25 30

Arg Ile Leu Leu Val Lys Tyr Ser Ala Asn Glu Gly Lys Leu Arg Leu
35 40 45

Gly Ile Cys Met Glu His Phe His Leu Ile Thr His Leu Ser Leu Ala
50 55 60

Phe Gly Ser Val Ile Tyr Asn Met Glu Ile Ile Met Pro Phe Ala Ser
65 70 75 80

Cys Glu

<210> 114
<211> 344
<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 114

```
Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Ser Val Leu Met
  1               5                  10                  15

Gly Leu Val Leu Ile Cys Val Cys Ser Lys Thr His Ser Leu Lys Gly
             20                  25                  30

Leu Ala Arg Gly Gly Ala Gln Ile Phe Ser Cys Ile Ile Pro Glu Cys
         35                  40                  45

Leu Gln Arg Ala Xaa His Gly Leu Leu His Tyr Leu Phe His Thr Arg
     50                  55                  60

Asn His Thr Phe Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr
 65                  70                  75                  80

Thr Glu Tyr Thr Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu
                 85                  90                  95

Ser Leu His Tyr Leu Leu Leu Pro Tyr Leu Leu Leu Gly Val Asn Leu
            100                 105                 110

Phe Phe Phe Thr Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys
        115                 120                 125

Ala Asn Glu Leu Leu Phe Leu His Val Tyr Glu Phe Asp Glu Val Met
    130                 135                 140

Phe Pro Lys Asn Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala
145                 150                 155                 160

Arg Ser Lys His Cys Ser Val Cys Asn Trp Cys Val His Arg Phe Asp
                165                 170                 175

His His Cys Val Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg
            180                 185                 190

Tyr Phe Leu Ile Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val
        195                 200                 205

Ala Ile Val Ser Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp
    210                 215                 220

Leu Tyr Gln Glu Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met
225                 230                 235                 240

Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg Ile
                245                 250                 255

Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly Gly
            260                 265                 270

Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn
```

```
        275                 280                 285

Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val
    290                 295                 300

Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser
305                 310                 315                 320

His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro
                325                 330                 335

Cys His Glu Arg Lys Lys Gln Glu
            340
```

<210> 115
<211> 181
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (110)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 115

```
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
  1               5                  10                  15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
             20                  25                  30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
         35                  40                  45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
     50                  55                  60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
 65                  70                  75                  80

Ser Leu Leu Gly Pro Phe Ile Lys Asn Gln Cys His Ser Ser Val Ile
                85                  90                  95

Pro Leu Ser Asp Ser Ala Thr Ser Lys Ala Arg Ala Leu Xaa Leu Pro
            100                 105                 110

Gly Arg Glu Thr Val Leu Ser Val Leu Pro Val Phe Ser Ser Pro Thr
        115                 120                 125

Leu Pro Arg Thr His Ala Leu Gly Asp Ser Leu Gly Val Pro Gly Leu
    130                 135                 140

Leu Val Cys Ser Glu Thr Ser Thr Leu Asn Asp His Trp Cys Cys Arg
145                 150                 155                 160

Arg Ala Gly Ala Tyr Ile Pro Ile Asn Arg Arg Phe Ser His Leu Met
                165                 170                 175
```

Pro Leu Ala Phe Ser
180

<210> 116
<211> 115
<212> PRT
<213> Homo sapiens

<400> 116
Met Pro Ser Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
1 5 10 15

Ser Phe Leu Cys Leu Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
20 25 30

Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
35 40 45

Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
50 55 60

Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
65 70 75 80

Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
85 90 95

Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
100 105 110

Gly Gly Ile
115

<210> 117
<211> 70
<212> PRT
<213> Homo sapiens

<400> 117
Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
35 40 45

Met Leu Ser Ile Ser Ala Val Val Met Ser Tyr Leu Gln Asn Pro Gln
50 55 60

Pro Met Thr Pro Pro Trp
65 70

<210> 118
<211> 63
<212> PRT
<213> Homo sapiens

<400> 118
Met Arg Asp Leu Ser Phe Leu Tyr Thr Leu Leu Trp Leu Pro Glu Ile
1 5 10 15

Trp Gln Ala Leu Ala Gly Gly Ile Arg Leu Asp Glu Val Glu Leu Leu
20 25 30

Glu Asn Glu Ala Val Leu Gly Glu Glu Met Arg Leu Tyr Arg Lys Ile
35 40 45

Asn Glu Val Val Leu Ser Gly Asn Glu Val Val Leu Gly Gly Lys
50 55 60

<210> 119
<211> 334
<212> PRT
<213> Homo sapiens

<400> 119
Met Gly Ile Phe Pro Gly Ile Ile Leu Ile Phe Leu Arg Val Lys Phe
1 5 10 15

Ala Thr Ala Ala Val Ile Val Ser Gly Val Ser Lys His Leu His Cys
20 25 30

Ile Ser His Gln Lys Ser Thr Thr Val Ser His Glu Met Ser Gly Leu
35 40 45

Asn Trp Lys Pro Phe Val Tyr Gly Gly Leu Ala Ser Ile Val Ala Glu
50 55 60

Phe Gly Thr Phe Pro Val Asp Leu Thr Lys Thr Arg Leu Gln Val Gln
65 70 75 80

Gly Gln Ser Ile Asp Ala Arg Phe Lys Glu Ile Lys Tyr Arg Gly Met
85 90 95

Phe His Ala Leu Phe Arg Ile Cys Lys Glu Glu Gly Val Leu Ala Leu
100 105 110

Tyr Ser Gly Ile Ala Pro Ala Leu Leu Arg Gln Ala Ser Tyr Gly Thr
115 120 125

Ile Lys Ile Gly Ile Tyr Gln Ser Leu Lys Arg Leu Phe Val Glu Arg
130 135 140

Leu Glu Asp Glu Thr Leu Leu Ile Asn Met Ile Cys Gly Val Val Ser
145 150 155 160

Gly Val Ile Ser Ser Thr Ile Ala Asn Pro Thr Asp Val Leu Lys Ile
165 170 175

Arg Met Gln Ala Gln Gly Ser Leu Phe Gln Gly Ser Met Ile Gly Ser

180 185 190

Phe Ile Asp Ile Tyr Gln Gln Glu Gly Thr Arg Gly Leu Trp Arg Gly
195 200 205

Val Val Pro Thr Ala Gln Arg Ala Ala Ile Val Val Gly Val Glu Leu
210 215 220

Pro Val Tyr Asp Ile Thr Lys Lys His Leu Ile Leu Ser Gly Met Met
225 230 235 240

Gly Asp Thr Ile Leu Thr His Phe Val Ser Ser Phe Thr Cys Gly Leu
245 250 255

Ala Gly Ala Leu Ala Ser Asn Pro Val Asp Val Val Arg Thr Arg Met
260 265 270

Met Asn Gln Arg Ala Ile Val Gly His Val Asp Leu Tyr Lys Gly Thr
275 280 285

Val Asp Gly Ile Leu Lys Met Trp Lys His Glu Gly Phe Phe Ala Leu
290 295 300

Tyr Lys Gly Phe Trp Pro Asn Trp Leu Arg Leu Gly Pro Trp Asn Ile
305 310 315 320

Ile Phe Phe Ile Thr Tyr Glu Gln Leu Lys Arg Leu Gln Ile
325 330

<210> 120
<211> 221
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 120
Met Ala Leu Ala Leu Ala Ala Leu Ala Ala Val Glu Pro Ala Cys Gly
1 5 10 15

Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu
20 25 30

Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile Ser Ala Glu
35 40 45

Ser Ala Xaa Tyr Phe Asp Tyr Lys Asp Glu Ser Gly Phe Pro Lys Pro
50 55 60

Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp Glu Ala Glu
65 70 75 80

Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly Arg Asp Glu
85 90 95

```
Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln Leu Arg Ile
            100                 105                 110

Gly Asn Asp Gly Ile Phe Met Leu Thr Phe Phe Met Ala Phe Leu Phe
        115                 120                 125

Asn Trp Ile Gly Phe Phe Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala
    130                 135                 140

Gly Arg Tyr Gly Ala Ile Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp
145                 150                 155                 160

Ile Leu Ile Val Arg Phe Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly
                165                 170                 175

Gln Tyr Trp Leu Trp Trp Val Phe Leu Val Leu Gly Phe Leu Leu Phe
            180                 185                 190

Leu Arg Gly Phe Ile Asn Tyr Ala Lys Val Arg Lys Met Pro Glu Thr
        195                 200                 205

Phe Ser Asn Leu Pro Arg Thr Arg Val Leu Phe Ile Tyr
    210                 215                 220
```

<210> 121
<211> 472
<212> PRT
<213> Homo sapiens

<400> 121

```
Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu Ser
  1               5                  10                  15

Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys Arg Thr
             20                  25                  30

Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp Val Ala Lys
         35                  40                  45

Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln Asn Arg Ser Tyr
     50                  55                  60

Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly Pro Arg Leu Ser Gly
 65                  70                  75                  80

Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile Met Tyr Gln Asn Leu Gln
                 85                  90                  95

Gln Asp Gly Leu Glu Lys Val His Leu Glu Pro Val Arg Ile Pro His
            100                 105                 110

Trp Glu Arg Gly Glu Glu Ser Ala Val Met Leu Glu Pro Arg Ile His
        115                 120                 125

Lys Ile Ala Ile Leu Gly Leu Gly Ser Ser Ile Gly Thr Pro Pro Glu
    130                 135                 140

Gly Ile Thr Ala Glu Val Leu Val Val Thr Ser Phe Asp Glu Leu Gln
```

```
145                 150                 155                 160

Arg Arg Ala Ser Glu Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro
                165                 170                 175

Tyr Ile Asn Tyr Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val
            180                 185                 190

Glu Ala Ala Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala
        195                 200                 205

Ser Phe Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp
    210                 215                 220

Gly Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
225                 230                 235                 240

Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln Leu
                245                 250                 255

Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn Thr Val
            260                 265                 270

Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val Leu Val Ser
        275                 280                 285

Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala Met Asp Asp Gly
    290                 295                 300

Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser Leu Ile Lys Asp Leu
305                 310                 315                 320

Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu Val Leu Trp Thr Ala Glu
                325                 330                 335

Glu Gln Gly Gly Val Gly Ala Phe Gln Tyr Tyr Gln Leu His Lys Val
            340                 345                 350

Asn Ile Ser Asn Tyr Ser Leu Val Met Glu Ser Asp Ala Gly Thr Phe
        355                 360                 365

Leu Pro Thr Gly Leu Gln Phe Thr Gly Ser Glu Lys Ala Arg Ala Ile
    370                 375                 380

Met Glu Glu Val Met Ser Leu Leu Gln Pro Leu Asn Ile Thr Gln Val
385                 390                 395                 400

Leu Ser His Gly Glu Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly
                405                 410                 415

Val Pro Gly Ala Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe
            420                 425                 430

His His Ser His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met
        435                 440                 445

Asn Val Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp
    450                 455                 460

Met Glu Glu Met Leu Pro Arg Ser
```

465 470

<210> 122
<211> 167
<212> PRT
<213> Homo sapiens

<400> 122
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
20 25 30

Pro Pro Ser Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly
35 40 45

Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu
50 55 60

Arg Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile
65 70 75 80

Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro
85 90 95

Ile Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp
100 105 110

Asp Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu
115 120 125

Ala Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Ala
130 135 140

Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Ser Val Phe
145 150 155 160

Asp Arg His Val Val Leu Ser
165

<210> 123
<211> 46
<212> PRT
<213> Homo sapiens

<400> 123
Met Lys Phe Ile Leu Trp Arg Arg Phe Arg Trp Ala Ile Ile Leu Phe
1 5 10 15

Ile Ile Leu Phe Ile Leu Leu Leu Phe Leu Ala Ile Phe Ile Tyr Ala
20 25 30

Phe Pro Asn Tyr Ala Ala Met Lys Leu Val Lys Pro Phe Ser
35 40 45

<210> 124
<211> 108
<212> PRT
<213> Homo sapiens

<400> 124
Met His Gln Asp Trp Leu Cys Asn Leu Gly Trp Pro Leu Leu Ser Leu
1 5 10 15

Trp Ala Ala Glu Ser Ala Pro His Val Ala Met Ala Ser Ala Thr Ala
20 25 30

Gln Leu Trp Ser Arg Pro Cys Gly Arg Thr His Met Val Ser Leu Ala
35 40 45

Leu Gly His Gln Glu Thr Gly Leu Trp Leu Cys Ser Ala Phe Gly Cys
50 55 60

Val Val Asp Ser Pro Trp Ala Ser Val Cys Pro Ser Val Lys Gly Gln
65 70 75 80

Leu Thr Val Cys Gly Ile Leu Pro Arg Val Pro Val Cys Val Tyr Val
85 90 95

Cys Ala Cys Val Arg Val Ser Met Cys Val His Ile
100 105

<210> 125
<211> 60
<212> PRT
<213> Homo sapiens

<400> 125
Met Arg Gly Cys Val Pro Ala Phe Leu Leu His Val Leu Ser Leu Arg
1 5 10 15

Arg Ala Cys Cys Thr Gln Ala Ala Gln Val Phe Thr Ala Gln Leu Pro
20 25 30

Gly Arg Gln Val Ala Arg Arg Arg Gly Gly Trp His Glu Gln Gln Gly
35 40 45

Gly Pro Met Leu Cys Ser Ser His His Ser Arg Thr
50 55 60

<210> 126
<211> 248
<212> PRT
<213> Homo sapiens

<400> 126
Met Ala Met Leu Pro Leu Val Leu His Trp Phe Phe Ile Glu Trp Tyr
1 5 10 15

```
Ser Gly Lys Lys Ser Ser Ser Ala Leu Phe Gln His Ile Thr Ala Leu
            20                  25                  30

Phe Glu Cys Ser Met Ala Ala Ile Ile Thr Leu Leu Val Ser Asp Pro
        35                  40                  45

Val Gly Val Leu Tyr Ile Arg Ser Cys Arg Val Leu Met Leu Ser Asp
    50                  55                  60

Trp Tyr Thr Met Leu Tyr Asn Pro Ser Pro Asp Tyr Val Thr Thr Val
65                  70                  75                  80

His Cys Thr His Glu Ala Val Tyr Pro Leu Tyr Thr Ile Val Phe Ile
                85                  90                  95

Tyr Tyr Ala Phe Cys Leu Val Leu Met Met Leu Leu Arg Pro Leu Leu
            100                 105                 110

Val Lys Lys Ile Ala Cys Gly Leu Gly Lys Ser Asp Arg Phe Lys Ser
        115                 120                 125

Ile Tyr Ala Ala Leu Tyr Phe Phe Pro Ile Leu Thr Val Leu Gln Ala
    130                 135                 140

Val Gly Gly Gly Leu Leu Tyr Tyr Ala Phe Pro Tyr Ile Ile Leu Val
145                 150                 155                 160

Leu Ser Leu Val Thr Leu Ala Val Tyr Met Ser Ala Ser Glu Ile Glu
                165                 170                 175

Asn Cys Tyr Asp Leu Leu Val Arg Lys Lys Arg Leu Ile Val Leu Phe
            180                 185                 190

Ser His Trp Leu Leu His Ala Tyr Gly Ile Ile Ser Ile Ser Arg Val
        195                 200                 205

Asp Lys Leu Glu Gln Asp Leu Pro Pro Leu Ala Leu Val Pro Thr Pro
    210                 215                 220

Ala Leu Phe Tyr Leu Phe Thr Ala Lys Phe Thr Glu Pro Ser Arg Ile
225                 230                 235                 240

Leu Ser Glu Gly Ala Asn Gly His
                245
```

<210> 127
<211> 248
<212> PRT
<213> Homo sapiens

<400> 127

```
Met Glu Lys Ile Pro Glu Ile Gly Lys Phe Gly Glu Lys Ala Pro Pro
  1               5                  10                  15

Ala Pro Ser His Val Trp Arg Pro Ala Ala Leu Phe Leu Thr Leu Leu
            20                  25                  30

Cys Leu Leu Leu Leu Ile Gly Leu Gly Val Leu Ala Ser Met Phe His
```

```
                                                    80
         35                  40                  45

Val Thr Leu Lys Ile Glu Met Lys Lys Met Asn Lys Leu Gln Asn Ile
     50                  55                  60

Ser Glu Glu Leu Gln Arg Asn Ile Ser Leu Gln Leu Met Ser Asn Met
 65                  70                  75                  80

Asn Ile Ser Asn Lys Ile Arg Asn Leu Ser Thr Thr Leu Gln Thr Ile
                 85                  90                  95

Ala Thr Lys Leu Cys Arg Glu Leu Tyr Ser Lys Glu Gln Glu His Lys
            100                 105                 110

Cys Lys Pro Cys Pro Arg Arg Trp Ile Trp His Lys Asp Ser Cys Tyr
        115                 120                 125

Phe Leu Ser Asp Asp Val Gln Thr Trp Gln Glu Ser Lys Met Ala Cys
    130                 135                 140

Ala Ala Gln Asn Ala Ser Leu Leu Lys Ile Asn Asn Lys Asn Ala Leu
145                 150                 155                 160

Glu Phe Ile Lys Ser Gln Ser Arg Ser Tyr Asp Tyr Trp Leu Gly Leu
                165                 170                 175

Ser Pro Glu Glu Asp Ser Thr Arg Gly Met Arg Val Asp Asn Ile Ile
            180                 185                 190

Asn Ser Ser Ala Trp Val Ile Arg Asn Ala Pro Asp Leu Asn Asn Met
        195                 200                 205

Tyr Cys Gly Tyr Ile Asn Arg Leu Tyr Val Gln Tyr Tyr His Cys Thr
    210                 215                 220

Tyr Lys Gln Arg Met Ile Cys Glu Lys Met Ala Asn Pro Val Gln Leu
225                 230                 235                 240

Gly Ser Thr Tyr Phe Arg Glu Ala
                245
```

<210> 128
<211> 612
<212> PRT
<213> Homo sapiens

```
<400> 128
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60
```

```
Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85                  90                  95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145                 150                 155                 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165                 170                 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180                 185                 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195                 200                 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210                 215                 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
                245                 250                 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380
```

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Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385                 390                 395                 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
                405                 410                 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
            420                 425                 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
        435                 440                 445

Cys Ser Asn Asp Cys Pro Arg Lys Ile Thr Pro Phe Gly Val Asn Gln
    450                 455                 460

Pro Gly Pro Tyr Ile Met Tyr Thr Thr Val Asp Ala Asn Gly Tyr Leu
465                 470                 475                 480

Lys Asn Gly Ser Ala Gly Gln Leu Ser Gln Ser Ala His Leu Ala Leu
                485                 490                 495

Gln Leu Pro Tyr Asn Val Leu Gly Leu Gly Arg Ser Ala Asn Phe Leu
            500                 505                 510

Asp His Leu Tyr Val Gly Ile Pro Arg Pro Ser Gly Glu Lys Ser Ile
        515                 520                 525

Arg Lys Gln Glu Trp Thr Ala Ile Ile Pro Asn Ser Gln Leu Ile Val
    530                 535                 540

Ile Pro Tyr Pro His Asn Val Pro Arg Ser Trp Ser Ala Lys Leu Tyr
545                 550                 555                 560

Leu Thr Pro Ser Asn Ile Val Leu Leu Thr Ala Ile Ala Leu Ile Gly
                565                 570                 575

Val Cys Val Phe Ile Leu Ala Ile Ile Gly Ile Leu His Trp Gln Glu
            580                 585                 590

Lys Lys Ala Asp Asp Arg Glu Lys Arg Gln Glu Ala His Arg Phe His
        595                 600                 605

Phe Asp Ala Met
    610
```

<210> 129
<211> 447
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (309)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (333)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 129

```
Met Glu Leu Ser Gln Met Ser Xaa Leu Met Gly Leu Ser Val Leu Leu
  1               5                  10                  15

Gly Leu Leu Ala Leu Met Ala Thr Ala Ala Val Xaa Arg Gly Trp Leu
            20                  25                  30

Arg Ala Gly Glu Glu Arg Ser Gly Arg Pro Ala Cys Gln Lys Ala Asn
         35                  40                  45

Gly Phe Pro Pro Asp Lys Ser Ser Gly Ser Lys Lys Gln Lys Gln Tyr
     50                  55                  60

Gln Arg Ile Arg Lys Glu Lys Pro Gln Gln His Asn Phe Thr His Arg
 65                  70                  75                  80

Leu Leu Ala Ala Ala Leu Lys Ser His Ser Gly Asn Ile Ser Cys Met
                85                  90                  95

Asp Phe Ser Ser Asn Gly Lys Tyr Leu Ala Thr Cys Ala Asp Asp Arg
            100                 105                 110

Thr Ile Arg Ile Trp Ser Thr Lys Asp Phe Leu Gln Arg Glu His Arg
        115                 120                 125

Ser Met Arg Ala Asn Val Glu Leu Asp His Ala Thr Leu Val Arg Phe
    130                 135                 140

Ser Pro Asp Cys Arg Ala Phe Ile Val Trp Leu Ala Asn Gly Asp Thr
145                 150                 155                 160

Leu Arg Val Phe Lys Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe
                165                 170                 175

Thr Ala Thr Pro Glu Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile
            180                 185                 190

Asp Ile Gly Ile Ala Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser
        195                 200                 205

Asp Thr Thr Val Leu Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr
    210                 215                 220

Ile Asn Thr Asn Gln Met Asn Asn Thr His Ala Ala Val Ser Pro Cys
225                 230                 235                 240

Gly Arg Phe Val Ala Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp
```

```
                245                 250                 255

Glu Val Cys Phe Gly Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala
            260                 265                 270

Phe Glu Leu Lys Gly His Ser Ala Ala Val His Ser Phe Ala Phe Ser
        275                 280                 285

Asn Asp Ser Arg Arg Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys
    290                 295                 300

Leu Trp Asp Thr Xaa Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu
305                 310                 315                 320

Leu Lys Thr Gly Arg Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg
                325                 330                 335

Leu Ala Leu Ser Pro Asn Ala Gln Val Leu Ala Leu Ala Ser Gly Ser
            340                 345                 350

Ser Ile His Leu Tyr Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe
        355                 360                 365

Glu Arg Val His Gly Glu Cys Ile Ala Asn Leu Ser Phe Asp Ile Thr
    370                 375                 380

Gly Arg Phe Leu Ala Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His
385                 390                 395                 400

Asn Thr Pro Gly His Arg Ala Met Val Glu Glu Met Gln Gly His Leu
                405                 410                 415

Lys Arg Ala Ser Asn Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu
            420                 425                 430

Thr Gln Ala Gln Glu Thr Leu Lys Ser Leu Gly Ala Leu Lys Lys
        435                 440                 445


<210> 130
<211> 291
<212> PRT
<213> Homo sapiens

<400> 130
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
  1               5                  10                  15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
             20                  25                  30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
         35                  40                  45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
     50                  55                  60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
 65                  70                  75                  80
```

```
His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
                85                  90                  95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
            100                 105                 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
        115                 120                 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
    130                 135                 140

Thr Leu Lys Glu Thr Pro Gly Thr Val Leu Glu Val Leu Ile Cys Phe
145                 150                 155                 160

Phe Thr Leu Trp Ser Val Val Gly Leu Thr Gly Phe His Thr Phe Leu
                165                 170                 175

Val Ala Leu Asn Gln Thr Thr Asn Glu Asp Ile Lys Gly Ser Trp Thr
            180                 185                 190

Gly Lys Asn Arg Val Gln Asn Pro Tyr Ser His Gly Asn Ile Val Lys
        195                 200                 205

Asn Cys Cys Glu Val Leu Cys Gly Pro Leu Pro Pro Ser Val Leu Asp
    210                 215                 220

Arg Arg Gly Ile Leu Pro Leu Glu Glu Ser Gly Ser Arg Pro Pro Ser
225                 230                 235                 240

Thr Gln Glu Thr Ser Ser Ser Leu Leu Pro Gln Ser Pro Ala Pro Thr
                245                 250                 255

Glu His Leu Asn Ser Asn Glu Met Pro Glu Asp Ser Ser Thr Pro Glu
            260                 265                 270

Glu Met Pro Pro Pro Glu Pro Pro Glu Pro Pro Gln Glu Ala Ala Glu
        275                 280                 285

Ala Glu Lys
    290
```

<210> 131
<211> 78
<212> PRT
<213> Homo sapiens

<400> 131

```
Met Val Arg Lys Trp Leu Thr Phe Val Glu His Leu Leu Cys Ala Trp
  1               5                  10                  15

Pro Arg Leu Gly Ala Phe Val Pro Arg Val Thr Pro Ser Glu Cys Ser
             20                  25                  30

Ser Leu Pro His Ser Asn Trp Gly Val Gly Gly Arg Ala Ala Gln Leu
         35                  40                  45
```

Thr Gly Ala Glu Leu Lys Thr His Ser Trp Val Cys Leu Gly Trp Ala
50 55 60

Val Leu Val Ala Pro Val Ala Asn Thr Arg Ala Pro Phe Thr
65 70 75

<210> 132
<211> 333
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (97)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 132
Met Leu Met Phe Ala Val Ile Val Ala Ser Ser Gly Leu Leu Leu Met
1 5 10 15

Ile Glu Arg Gly Ile Leu Ala Glu Met Lys Pro Leu Pro Leu His Pro
20 25 30

Pro Gly Arg Glu Gly Thr Ala Trp Arg Gly Lys Ala Pro Lys Pro Gly
35 40 45

Gly Leu Ser Leu Arg Ala Gly Asp Ala Asp Leu Gln Val Arg Gln Asp
50 55 60

Val Arg Asn Arg Thr Leu Arg Ala Val Cys Gly Gln Pro Gly Met Pro
65 70 75 80

Arg Asp Pro Trp Asp Leu Pro Val Gly Gln Arg Arg Thr Leu Leu Arg
85 90 95

Xaa Ile Leu Val Ser Asp Arg Tyr Arg Phe Leu Tyr Cys Tyr Val Pro
100 105 110

Lys Val Ala Cys Ser Asn Trp Lys Arg Val Met Lys Val Leu Ala Gly
115 120 125

Val Leu Asp Ser Val Asp Val Arg Leu Lys Met Asp His Arg Ser Asp
130 135 140

Leu Val Phe Leu Ala Asp Leu Arg Pro Glu Glu Ile Arg Tyr Arg Leu
145 150 155 160

Gln His Tyr Phe Lys Phe Leu Phe Val Arg Glu Pro Leu Glu Arg Leu
165 170 175

Leu Ser Ala Tyr Arg Asn Lys Phe Gly Glu Ile Arg Glu Tyr Gln Gln
180 185 190

Arg Tyr Gly Ala Glu Ile Val Arg Arg Tyr Arg Ala Gly Ala Gly Pro
195 200 205

Ser Pro Ala Gly Asp Asp Val Thr Phe Pro Glu Phe Leu Arg Tyr Leu
210 215 220

```
Val Asp Glu Asp Pro Glu Arg Met Asn Glu His Trp Met Pro Val Tyr
225                 230                 235                 240

His Leu Cys Gln Pro Cys Ala Val His Tyr Asp Phe Val Gly Ser Tyr
                245                 250                 255

Glu Arg Leu Glu Ala Asp Ala Asn Gln Val Leu Glu Trp Val Arg Ala
            260                 265                 270

Pro Pro His Val Arg Phe Pro Ala Arg Gln Ala Trp Tyr Arg Pro Ala
        275                 280                 285

Ser Pro Glu Ser Leu His Tyr His Leu Cys Ser Ala Pro Arg Ala Leu
    290                 295                 300

Leu Gln Asp Val Leu Pro Lys Tyr Ile Leu Asp Phe Ser Leu Phe Ala
305                 310                 315                 320

Tyr Pro Leu Pro Asn Val Thr Lys Glu Ala Cys Gln Gln
                325                 330
```

<210> 133
<211> 164
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (126)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 133

```
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
  1               5                  10                  15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
            20                  25                  30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
        35                  40                  45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
    50                  55                  60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65                  70                  75                  80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
                85                  90                  95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
            100                 105                 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Xaa Ser Met
        115                 120                 125

Asn Ala Phe Pro Ala Pro Ser Pro Thr Cys Thr Pro Glu Pro Leu Gly
```

130 135 140

Ser Val Cys Leu Pro Ser Thr Ser Val Ser Leu Pro Ser His Leu Pro
145 150 155 160

Gly Ser Leu Gln

<210> 134
<211> 244
<212> PRT
<213> Homo sapiens

<400> 134
Met Val Ala Val Gly Val Tyr Ala Arg Leu Met Lys His Ala Glu Ala
1 5 10 15

Ala Leu Ala Cys Leu Ala Val Asp Pro Ala Ile Leu Leu Ile Val Val
20 25 30

Gly Val Leu Met Phe Leu Leu Thr Phe Cys Gly Cys Ile Gly Ser Leu
35 40 45

Arg Glu Asn Ile Cys Leu Leu Gln Thr Phe Ser Leu Cys Leu Thr Ala
50 55 60

Val Phe Leu Leu Gln Leu Ala Ala Gly Ile Leu Gly Phe Val Phe Ser
65 70 75 80

Asp Lys Ala Arg Gly Lys Val Ser Glu Ile Ile Asn Asn Ala Ile Val
85 90 95

His Tyr Arg Asp Asp Leu Asp Leu Gln Asn Leu Ile Asp Phe Gly Gln
100 105 110

Lys Lys Phe Ser Cys Cys Gly Gly Ile Ser Tyr Lys Asp Trp Ser Gln
115 120 125

Asn Met Tyr Phe Asn Cys Ser Glu Asp Asn Pro Ser Arg Glu Arg Cys
130 135 140

Ser Val Pro Tyr Ser Cys Cys Leu Pro Thr Pro Asp Gln Ala Val Ile
145 150 155 160

Asn Thr Met Cys Gly Gln Gly Met Gln Ala Phe Asp Tyr Leu Glu Ala
165 170 175

Ser Lys Val Ile Tyr Thr Asn Gly Cys Ile Asp Lys Leu Val Asn Trp
180 185 190

Ile His Ser Asn Leu Phe Leu Leu Gly Gly Val Ala Leu Gly Leu Ala
195 200 205

Ile Pro Gln Leu Val Gly Ile Leu Leu Ser Gln Ile Leu Val Asn Gln
210 215 220

Ile Lys Asp Gln Ile Lys Leu Gln Leu Tyr Asn Gln Gln His Arg Ala
225 230 235 240

Asp Pro Trp Tyr

<210> 135
<211> 55
<212> PRT
<213> Homo sapiens

<400> 135
Met Gly Thr Val Gly Leu Trp Pro Ser Trp Leu Trp Leu Pro Ala Ser
1 5 10 15

Trp Pro Leu Thr Ser Cys Gly Val Thr Arg Arg Arg Leu Arg Gly Pro
20 25 30

Gly Leu Arg Arg Thr Ser Gln Thr Gly Arg His Thr Ser Pro Cys Pro
35 40 45

Thr Ala Thr Trp Ala Glu Ser
50 55

<210> 136
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 136
Met Ser Ile Val Met Ser Pro Leu Leu Leu Pro Ile Cys Tyr Leu Asn
1 5 10 15

Leu Leu Leu Phe Phe Val Asn Leu Ala Lys Asn Leu Ser Ile Leu Phe
20 25 30

Val Ser Ser Lys Lys Tyr Thr Phe Val Phe Met Ile Ser Leu Xaa Phe
35 40 45

Phe His Xaa Tyr Phe Ile
50

<210> 137
<211> 88
<212> PRT
<213> Homo sapiens

<400> 137
Met Ala Ile Ile Ser Phe Glu Leu Leu Phe Leu Met Asn Leu Pro Thr
1 5 10 15

Val Asn Ser Ser Asn Phe Lys Leu Ile Ile Pro Glu Asp Val Thr Leu
20 25 30

Ser Phe Val Ser His Leu Asp Ile Thr Val Asn His Phe Val Phe Leu
35 40 45

Ser Thr Phe Glu Leu Ala Gly Val Ile Glu Gly Lys Pro Leu Pro Asp
50 55 60

Ser Lys Ser Asp Leu Cys Pro Ile Leu Gly Gln Leu Trp Phe His Ile
65 70 75 80

Leu Leu Phe Phe Ile Phe Trp Val
85

<210> 138
<211> 61
<212> PRT
<213> Homo sapiens

<400> 138
Met Arg Leu Pro Ile Ala Pro His Leu Gln Tyr Phe Met Trp Ser Val
1 5 10 15

Leu Leu Phe Leu Val Ile Leu Val Asp Met Lys Trp His Leu Ser Val
20 25 30

Ala Phe His Tyr Ile Ser Leu Met Thr Asn Gly Ile Leu Ser Pro Phe
35 40 45

Gln Cys Leu Leu Ala Ile His Val Ser Leu Phe Phe Val
50 55 60

<210> 139
<211> 105
<212> PRT
<213> Homo sapiens

<400> 139
Met Cys Leu Leu Pro Gly Gly Val Leu Leu Ile Trp Ser Cys Ala Ser
1 5 10 15

Gly Thr Pro Ala Ser His Thr Lys Asp Trp Gly Arg Cys Lys Phe Ser
20 25 30

Ala Ala Thr Lys Arg Thr Ala Glu Ser Asn Leu Glu Ser Thr Gln Leu
35 40 45

Met Leu Ala Ser Gln Ile Asp Pro Leu Leu Ala Glu Cys Trp His Leu
50 55 60

Cys Ala Ser Val Ser Ser Ser Val Asn Gly Gly Asp Lys Lys Cys Val
65 70 75 80

His Thr Ser Arg Ala Val Gly Arg Ile Lys Leu Cys Ser Asp Thr Ile
85 90 95

Arg Ala Cys Ser Gly Trp Tyr Leu Gln
100 105

<210> 140
<211> 51
<212> PRT
<213> Homo sapiens

<400> 140
Met Ser His Ser Val Phe Ala His Tyr Ile Phe Asn Ile Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Ile Gly Phe Leu Tyr Ser Met Pro Phe Ile
20 25 30

Tyr Lys Asp Thr Lys Lys Thr His Val Cys Asn Phe Asn Asn Ile Phe
35 40 45

Pro Ile Leu
50

<210> 141
<211> 119
<212> PRT
<213> Homo sapiens

<400> 141
Met Lys Trp Arg Arg Lys Ser Ala Tyr Trp Lys Ala Leu Lys Val Phe
1 5 10 15

Lys Leu Pro Val Glu Phe Leu Leu Leu Leu Thr Val Pro Val Val Asp
20 25 30

Pro Asp Lys Asp Asp Gln Asn Trp Lys Arg Pro Leu Asn Cys Leu His
35 40 45

Leu Val Ile Ser Pro Leu Val Val Val Leu Thr Leu Gln Ser Gly Thr
50 55 60

Tyr Gly Val Tyr Glu Ile Gly Gly Leu Val Pro Val Trp Val Val Val
65 70 75 80

Val Ile Ala Gly Thr Ala Leu Ala Ser Val Thr Phe Phe Ala Thr Ser
85 90 95

Asp Ser Gln Pro Pro Arg Leu His Trp Leu Phe Ala Phe Leu Gly Phe
100 105 110

Leu Thr Ser Ala Leu Trp Ile
115

<210> 142
<211> 58
<212> PRT
<213> Homo sapiens

<400> 142
Met Cys Ser Gly Ser Phe Lys Glu Leu Tyr Leu Val Pro Ile Ser Leu
1 5 10 15

Phe Ser Thr Cys Val Leu Gly Phe Tyr Phe His Asn Phe Leu Leu Leu
20 25 30

Ile Ile Leu Phe Ser Ile Leu Leu Arg Lys Ile Thr Gly Lys Leu Phe
35 40 45

Phe Thr Tyr Tyr His Phe Ser Cys Gly Val
50 55

<210> 143
<211> 99
<212> PRT
<213> Homo sapiens

<400> 143

Met Leu Phe Phe Leu Ser Leu Phe Leu Ser Leu Leu Leu Thr Leu Ser
1 5 10 15

Leu Pro Ser Phe Leu Pro Phe Ser Phe Phe Phe Phe Ser Leu Phe Pro
20 25 30

His Leu Ser Ala Cys Leu Leu Pro Ser Leu Pro Ser Pro Pro Phe Pro
35 40 45

Leu Pro Pro Ser Leu Pro Ser Phe Leu Pro Ser Phe Leu Pro Ser Phe
50 55 60

Leu Pro Ser Leu Leu Ser Pro Ser Phe Pro Ala Phe Phe Pro Ser Phe
65 70 75 80

Cys Gln Leu Ala Arg Arg Ser Pro Arg Lys Ser Thr Gln Met Leu Gln
85 90 95

Ser Thr Ser

<210> 144
<211> 64
<212> PRT
<213> Homo sapiens

<220>
<221> SITE

<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 144
Met Ala Val Leu Leu Ile Thr Ile Leu Leu Phe Leu Cys Leu Gly Tyr
1 5 10 15

Tyr Arg Val Ile Thr Glu Ile Ser Arg Lys Thr Pro Ala Cys Arg Met
20 25 30

Phe Thr Ser Ser Leu Ser Ser Trp Tyr Ile Met Arg Lys Leu Tyr Asp
35 40 45

Thr Pro Gly Glu Val Phe Leu Ser His Ala Ile Val Xaa Phe Leu Lys
50 55 60

<210> 145
<211> 66
<212> PRT
<213> Homo sapiens

<400> 145
Met Leu Asn Gln Pro Cys Ile Leu Gly Met Lys Pro Thr Trp Leu Trp
1 5 10 15

Trp Ile Ser Phe Leu Met Cys Cys Trp Val Trp Leu Ala Ser Val Leu
20 25 30

Leu Gly Ile Phe Ala Ser Ile Phe Ile Arg Asp Ile Gly Leu Glu Phe
35 40 45

Ser Phe Phe Val Met Cys Leu Pro Gly Phe Gly Ile Arg Val Met Leu
50 55 60

Ala Ser
65

<210> 146
<211> 58
<212> PRT
<213> Homo sapiens

<400> 146
Met Thr Ala Met Ser Ile His Leu Phe Cys Thr Ala Leu Ser Cys Gly
1 5 10 15

Ser Ser Gly Gln Cys Asn Lys Ala Ile Lys Arg Asn Lys Ile Ser Asn
20 25 30

Asp Trp Lys Asp Val Asn Val Ser Ser Phe Ile Glu Asn Met Ile His
35 40 45

Arg Tyr Thr Tyr Thr Asn Ala Leu Asn Ser

50 55

<210> 147
<211> 55
<212> PRT
<213> Homo sapiens

<400> 147
Met Ser His Cys Thr Trp Pro Val Cys Leu Phe Cys Leu Val Pro Pro
1 5 10 15

Pro Met Gly Asp Leu Lys Glu Val Cys Leu Pro His Arg Cys Pro Gly
20 25 30

Arg Thr Ala Cys Cys Ser Tyr Ser Glu Pro His Leu Gln Thr Glu Glu
35 40 45

Asp Arg Arg Thr Leu Ile Cys
50 55

<210> 148
<211> 65
<212> PRT
<213> Homo sapiens

<400> 148
Met Thr Asn Gly His Gln Val Leu Leu Leu Leu Leu Leu Thr Ser Ala
1 5 10 15

Val Ala Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp
20 25 30

Met Cys Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu
35 40 45

Gly Gly Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly
50 55 60

Tyr
65

<210> 149
<211> 327
<212> PRT
<213> Homo sapiens

<400> 149
Met Ala Cys Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg
1 5 10 15

His Leu Pro Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn
20 25 30

Phe Gln Glu Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val

```
                                                95
         35                  40                  45

Leu Gly Leu Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His
     50                  55                  60

Gln Gly Ala Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu
 65                  70                  75                  80

Asn Tyr Arg Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe
                 85                  90                  95

Val Gln Phe Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile
            100                 105                 110

Ser Phe Leu Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp
        115                 120                 125

Asn Ser Asp Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu
    130                 135                 140

Pro Ser Arg Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu
145                 150                 155                 160

Glu Glu Ser Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe
                165                 170                 175

Thr Pro Leu Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser
            180                 185                 190

Arg Gly Gln Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp
        195                 200                 205

Glu Met Ser Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn
    210                 215                 220

Leu Gln Arg Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala
225                 230                 235                 240

Phe Ser Leu Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala
                245                 250                 255

Ala Phe Leu Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu
            260                 265                 270

Val Val Gln Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys
        275                 280                 285

Gln Glu His Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met
    290                 295                 300

Tyr Gly Gln Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile
305                 310                 315                 320

Leu His Met Glu Ala Val Met
                325
```

<210> 150
<211> 89

<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (10)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 150
Met Gly Phe Leu Gln Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His
1 5 10 15

Arg Val Ala Gly Ala Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu
20 25 30

Ile Glu Phe Ser Val Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro
35 40 45

Phe Pro Glu Glu Ala Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe
50 55 60

Leu Ile Phe Gln Ile His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe
65 70 75 80

Ser Pro Arg Arg Arg Ser Pro Thr Met
85

<210> 151
<211> 148
<212> PRT
<213> Homo sapiens

<400> 151
Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly Val Gly
1 5 10 15

Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro Ala Leu
20 25 30

Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala Ser Pro
35 40 45

Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln Cys Pro
50 55 60

Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala Gly Ala
65 70 75 80

Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala Gln Arg
85 90 95

Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala Ser Gly
100 105 110

```
Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr Thr Pro
        115                 120                 125

Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro Ala Leu
    130                 135                 140

Thr Leu Pro Pro
145
```

<210> 152
<211> 390
<212> PRT
<213> Homo sapiens

<400> 152

```
Met Leu Pro Thr Trp Trp Ile Val Ser Ser Trp Leu Val Trp Gly Val
  1               5                  10                  15

Ile Leu Phe Val Tyr Leu Val Ile Arg Ala Leu Arg Leu Trp Arg Thr
             20                  25                  30

Ala Lys Leu Gln Val Thr Leu Lys Lys Tyr Ser Val His Leu Glu Asp
         35                  40                  45

Met Ala Thr Asn Ser Arg Ala Phe Thr Asn Leu Val Arg Lys Ala Leu
     50                  55                  60

Arg Leu Ile Gln Glu Thr Glu Val Ile Ser Arg Gly Phe Thr Leu Val
 65                  70                  75                  80

Ser Ala Ala Cys Pro Phe Asn Lys Ala Gly Gln His Pro Ser Gln His
                 85                  90                  95

Leu Ile Gly Leu Arg Lys Ala Val Tyr Arg Thr Leu Arg Ala Asn Phe
            100                 105                 110

Gln Ala Ala Arg Leu Ala Thr Leu Tyr Met Leu Lys Asn Tyr Pro Leu
        115                 120                 125

Asn Ser Glu Ser Asp Asn Val Thr Asn Tyr Ile Cys Val Val Pro Phe
    130                 135                 140

Lys Glu Leu Gly Leu Gly Leu Ser Glu Glu Gln Ile Ser Glu Glu Glu
145                 150                 155                 160

Ala His Asn Phe Thr Asp Gly Phe Ser Leu Pro Ala Leu Lys Val Leu
                165                 170                 175

Phe Gln Leu Trp Val Ala Gln Ser Ser Glu Phe Phe Arg Arg Leu Ala
            180                 185                 190

Leu Leu Leu Ser Thr Ala Asn Ser Pro Pro Gly Pro Leu Leu Thr Pro
        195                 200                 205

Ala Leu Leu Pro His Arg Ile Leu Ser Asp Val Thr Gln Gly Leu Pro
    210                 215                 220
```

```
His Ala His Ser Ala Cys Leu Glu Glu Leu Lys Arg Ser Tyr Glu Phe
225                 230                 235                 240

Tyr Arg Tyr Phe Glu Thr Gln His Gln Ser Val Pro Gln Cys Leu Ser
                245                 250                 255

Lys Thr Gln Gln Lys Ser Arg Glu Leu Asn Asn Val His Thr Ala Val
            260                 265                 270

Arg Ser Leu Gln Leu His Leu Lys Ala Leu Leu Asn Glu Val Ile Ile
        275                 280                 285

Leu Glu Asp Glu Leu Glu Lys Leu Val Cys Thr Lys Glu Thr Gln Glu
    290                 295                 300

Leu Val Ser Glu Ala Tyr Pro Ile Leu Glu Gln Lys Leu Lys Leu Ile
305                 310                 315                 320

Gln Pro His Val Gln Ala Ser Asn Asn Cys Trp Glu Glu Ala Ile Ser
                325                 330                 335

Gln Val Asp Lys Leu Leu Arg Arg Asn Thr Asp Lys Lys Gly Lys Pro
            340                 345                 350

Glu Ile Ala Cys Glu Asn Pro His Cys Thr Val Ser Thr Phe Glu Ala
        355                 360                 365

Ala Tyr Ser Thr His Cys Arg Gln Arg Ser Asn Pro Arg Gly Ala Gly
    370                 375                 380

Ile Arg Ser Leu Cys Arg
385                 390
```

<210> 153
<211> 98
<212> PRT
<213> Homo sapiens

```
<400> 153
Met Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met
  1               5                  10                  15

Ser Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser
             20                  25                  30

Leu Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp
         35                  40                  45

Asn Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu
     50                  55                  60

Gly Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr
 65                  70                  75                  80

Gln Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu
                 85                  90                  95
```

Val Thr

<210> 154
<211> 60
<212> PRT
<213> Homo sapiens

<400> 154
Met Ser His Cys Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser
1 5 10 15

Cys Phe Trp Ala Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val
20 25 30

Ser Phe Arg Pro Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe
35 40 45

Ile Leu Arg Ile Leu Ile Leu Leu Arg Ser Phe Leu
50 55 60

<210> 155
<211> 392
<212> PRT
<213> Homo sapiens

<400> 155
Met Glu Trp Trp Ala Ser Ser Pro Leu Arg Leu Trp Leu Leu Leu Phe
1 5 10 15

Leu Leu Pro Ser Ala Gln Gly Arg Gln Lys Glu Ser Gly Ser Lys Trp
20 25 30

Lys Val Phe Ile Asp Gln Ile Asn Arg Ser Leu Glu Asn Tyr Glu Pro
35 40 45

Cys Ser Ser Gln Asn Cys Ser Cys Tyr His Gly Val Ile Glu Glu Asp
50 55 60

Leu Thr Pro Phe Arg Gly Gly Ile Ser Arg Lys Met Met Ala Glu Val
65 70 75 80

Val Arg Arg Lys Leu Gly Thr His Tyr Gln Ile Thr Lys Asn Arg Leu
85 90 95

Tyr Arg Glu Asn Asp Cys Met Phe Pro Ser Arg Cys Ser Gly Val Glu
100 105 110

His Phe Ile Leu Glu Val Ile Gly Arg Leu Pro Asp Met Glu Met Val
115 120 125

Ile Asn Val Arg Asp Tyr Pro Gln Val Pro Lys Trp Met Glu Pro Ala
130 135 140

Ile Pro Val Phe Ser Phe Ser Lys Thr Ser Glu Tyr His Asp Ile Met
145 150 155 160

```
Tyr Pro Ala Trp Thr Phe Trp Glu Gly Gly Pro Ala Val Trp Pro Ile
                165                 170                 175

Tyr Pro Thr Gly Leu Gly Arg Trp Asp Leu Phe Arg Glu Asp Leu Val
            180                 185                 190

Arg Ser Ala Ala Gln Trp Pro Trp Lys Lys Lys Asn Ser Thr Ala Tyr
        195                 200                 205

Phe Arg Gly Ser Arg Thr Ser Pro Glu Arg Asp Pro Leu Ile Leu Leu
    210                 215                 220

Ser Arg Lys Asn Pro Lys Leu Val Asp Ala Glu Tyr Thr Lys Asn Gln
225                 230                 235                 240

Ala Trp Lys Ser Met Lys Asp Thr Leu Gly Lys Pro Ala Ala Lys Asp
                245                 250                 255

Val His Leu Val Asp His Cys Lys Tyr Lys Tyr Leu Phe Asn Phe Arg
            260                 265                 270

Gly Val Ala Ala Ser Phe Arg Phe Lys His Leu Phe Leu Cys Gly Ser
        275                 280                 285

Leu Val Phe His Val Gly Asp Glu Trp Leu Glu Phe Phe Tyr Pro Gln
    290                 295                 300

Leu Lys Pro Trp Val His Tyr Ile Pro Val Lys Thr Asp Leu Ser Asn
305                 310                 315                 320

Val Gln Glu Leu Leu Gln Phe Val Lys Ala Asn Asp Asp Val Ala Gln
                325                 330                 335

Glu Ile Ala Glu Arg Gly Ser Gln Phe Ile Arg Asn His Leu Gln Met
            340                 345                 350

Asp Asp Ile Thr Cys Tyr Trp Glu Asn Leu Leu Ser Glu Tyr Ser Lys
        355                 360                 365

Phe Leu Ser Tyr Asn Val Thr Arg Arg Lys Gly Tyr Asp Gln Ile Ile
    370                 375                 380

Pro Lys Met Leu Lys Thr Glu Leu
385                 390
```

<210> 156
<211> 74
<212> PRT
<213> Homo sapiens

<400> 156

```
Met Leu Ile Leu Phe Leu Ser Val Cys Leu Phe Val Phe Leu Leu Thr
  1               5                  10                  15

Val Arg Ala Leu Cys Cys Arg Ser Ala Gly Val Trp Leu Arg Ser Thr
             20                  25                  30
```

Pro Asp Pro Val Cys Leu Gly Phe Ala Arg Gly Gly Cys Arg Ile Ala
35 40 45

Met Ile Ala Ala Cys Phe Ser Ser Gly Ser Phe Val Pro Glu Gly His
50 55 60

Pro Pro Asp Ala Ser Gln Ser Ser Pro Val
65 70

<210> 157
<211> 81
<212> PRT
<213> Homo sapiens

<400> 157
Met Trp Pro Leu Leu Ala Val Ser Pro Phe Gly Leu Val Trp Ala Ser
1 5 10 15

Ser Gln Ser Gly Ser Leu Leu Leu Arg Ala Ser Ile Pro Arg Gln His
20 25 30

Ser Arg Arg Ala Trp His Phe Tyr Ser Glu Val Trp Gln Ser His Ser
35 40 45

Val Ala Ser Val Leu Leu Tyr Leu Leu Val Arg Ala Ile Thr Lys Met
50 55 60

Cys Ile Gly Ser Lys Lys Arg Asp Ile Thr Pro Thr Thr Arg Trp Lys
65 70 75 80

Lys

<210> 158
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (49)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 158
Met Ser His His Ala Gly Leu Gly Gly Gly Ile Leu Phe Ser Leu Lys
1 5 10 15

Ile Ser Phe Phe Ile Ala Leu Ala Val Val Gly Gly Ser Arg Gly Val
20 25 30

Asn Asp Cys Gln Leu Gly Gly Cys Arg Val Gly Ser Cys Pro Arg Val
35 40 45

Xaa Val Arg Val Ala
50

<210> 159
<211> 102
<212> PRT
<213> Homo sapiens

<400> 159
Met Thr Val Arg Arg Leu Ser Leu Leu Cys Arg Asp Leu Trp Ala Leu
1 5 10 15

Trp Leu Leu Leu Lys Ala Gly Ala Val Arg Gly Ala Arg Ala Gly Pro
20 25 30

Arg Leu Pro Gly Arg Cys Cys Gly Ala Thr Cys Gly Asp Ala Gly Arg
35 40 45

Gly Trp Thr Phe Trp Ala Gln Pro Cys Pro Gln Lys Leu Leu Gly Gln
50 55 60

Lys Pro Gly Ala Gly Gly Cys Arg Gly Trp Val Leu Gly Trp Val Pro
65 70 75 80

Pro Arg Pro Glu Glu Pro Cys Ser Leu Ala Gly Lys Val Cys Thr Gly
85 90 95

Leu Ala Arg Trp Met Val
100

<210> 160
<211> 575
<212> PRT
<213> Homo sapiens

<400> 160
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr
35 40 45

Met Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser
50 55 60

Thr Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp
65 70 75 80

Leu Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly
85 90 95

Gln Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro
100 105 110

Ser Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly
115 120 125

```
Pro Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser
    130                 135                 140

Ala Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala
145                 150                 155                 160

Leu Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu
                165                 170                 175

Asp Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp
            180                 185                 190

Ala His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser
        195                 200                 205

Tyr Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly
    210                 215                 220

Ala Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys
225                 230                 235                 240

His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser
                245                 250                 255

Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp
            260                 265                 270

Val Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His
        275                 280                 285

Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu
    290                 295                 300

Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn
305                 310                 315                 320

Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro
                325                 330                 335

Trp Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg
            340                 345                 350

Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro
        355                 360                 365

Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg
    370                 375                 380

Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr
385                 390                 395                 400

Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn
                405                 410                 415

Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro
            420                 425                 430

Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr
        435                 440                 445
```

```
Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe
    450                 455                 460

Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln
465                 470                 475                 480

Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val
                485                 490                 495

Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr
            500                 505                 510

Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg
        515                 520                 525

Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr
    530                 535                 540

Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His
545                 550                 555                 560

Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
                565                 570                 575
```

<210> 161
<211> 643
<212> PRT
<213> Homo sapiens

```
<400> 161
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
  1               5                  10                  15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
             20                  25                  30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
         35                  40                  45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
     50                  55                  60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
 65                  70                  75                  80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr
                 85                  90                  95

Leu Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His
            100                 105                 110

Gly Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys
        115                 120                 125

Thr Lys Ala Lys Leu Trp Leu Ala Lys Arg Gln Asn Pro Cys Leu Val
    130                 135                 140
```

```
Thr Arg Ala Val Tyr Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu
145                 150                 155                 160

Asn Arg Ser Ala Lys Asp Asn Gln Pro Val Leu Glu Ser Leu Gly Phe
                165                 170                 175

Trp Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly
            180                 185                 190

Phe Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser
        195                 200                 205

Leu Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser
    210                 215                 220

Gly Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu
225                 230                 235                 240

Ser Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu
                245                 250                 255

Lys Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro
            260                 265                 270

Leu Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu
        275                 280                 285

Asn His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met
    290                 295                 300

Asp Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr
305                 310                 315                 320

Pro Lys Glu Phe Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg
                325                 330                 335

Ser Glu Ile Gln Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser
            340                 345                 350

His His Met Gln Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu
        355                 360                 365

Leu Lys Gln Trp Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu
    370                 375                 380

Pro Thr Glu Ser Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr
385                 390                 395                 400

Pro Leu Phe Leu Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr
                405                 410                 415

Leu Ala Leu Trp Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln
            420                 425                 430

Ala Val Arg Asp Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln
        435                 440                 445

Glu Asn Thr Cys Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala
    450                 455                 460
```

```
Ser Ile Ala Leu Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln
465                 470                 475                 480

Gln Trp Asp Gln Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu
                485                 490                 495

Leu Gly Glu Ser Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln
            500                 505                 510

Val Glu Glu Asp Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala
        515                 520                 525

Glu Thr Leu Ile Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu
    530                 535                 540

Leu Ser Lys Ser Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His
545                 550                 555                 560

Leu Gln Arg Met Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe
                565                 570                 575

Arg Glu Leu Pro Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr
            580                 585                 590

Arg Leu Arg Ile Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu
        595                 600                 605

Ala Phe Leu Glu Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val
    610                 615                 620

Trp Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu
625                 630                 635                 640

Ala Ala Cys
```

<210> 162
<211> 190
<212> PRT
<213> Homo sapiens

<400> 162

```
Met Ser Ser Gly Thr Glu Leu Leu Trp Pro Gly Ala Ala Leu Leu Val
  1               5                  10                  15

Leu Leu Gly Val Ala Ala Ser Leu Cys Val Arg Cys Ser Arg Pro Gly
             20                  25                  30

Ala Lys Arg Ser Glu Lys Ile Tyr Gln Gln Arg Ser Leu Arg Glu Asp
         35                  40                  45

Gln Gln Ser Phe Thr Gly Ser Arg Thr Tyr Ser Leu Val Gly Gln Ala
     50                  55                  60

Trp Pro Gly Pro Leu Ala Asp Met Ala Pro Thr Arg Lys Asp Lys Leu
 65                  70                  75                  80

Leu Gln Phe Tyr Pro Ser Leu Glu Asp Pro Ala Ser Ser Arg Tyr Gln
```

85 90 95

Asn Phe Ser Lys Gly Ser Arg His Gly Ser Glu Glu Ala Tyr Ile Asp
100 105 110

Pro Ile Ala Met Glu Tyr Tyr Asn Trp Gly Arg Phe Ser Lys Pro Pro
115 120 125

Glu Asp Asp Asp Ala Asn Ser Tyr Glu Asn Val Leu Ile Cys Lys Gln
130 135 140

Lys Thr Thr Glu Thr Gly Ala Gln Gln Glu Gly Ile Gly Gly Leu Cys
145 150 155 160

Arg Gly Asp Leu Ser Leu Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser
165 170 175

Gly Leu Cys Pro Ser Ala Ser Pro Glu Glu Asp Glu Gly Ile
180 185 190

<210> 163
<211> 63
<212> PRT
<213> Homo sapiens

<400> 163
Met Lys His Val Leu Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu
1 5 10 15

Leu Ser Ile Phe Val Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu
20 25 30

Ser Pro Ser Pro Gly Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn
35 40 45

Thr Glu Pro Thr Lys Gly Leu Pro Asp His Pro Ser Arg Ser Met
50 55 60

<210> 164
<211> 117
<212> PRT
<213> Homo sapiens

<400> 164
Met Ile Phe Leu Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser
1 5 10 15

Gly Phe Tyr His Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu
20 25 30

Ala Leu Phe Phe Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln
35 40 45

Leu Phe Cys Glu Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe
50 55 60

Val Ser Leu Phe Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala
65 70 75 80

Gly Leu Phe Ile Val Leu Pro Ser Asp Val Phe Phe Ser Val His His
85 90 95

Leu Glu Ala Pro Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu
100 105 110

Ile Ile Leu Leu Arg
115

<210> 165
<211> 42
<212> PRT
<213> Homo sapiens

<400> 165
Met Leu Leu Gln Phe Thr Leu Trp Val Phe Gly Ala Ile His Phe Pro
1 5 10 15

Lys Cys Leu Gly Ile Lys Glu Glu Leu Leu Lys Cys Cys Leu Gln Leu
20 25 30

Pro Pro Ser Ser Thr Tyr Glu Lys Val Val
35 40

<210> 166
<211> 47
<212> PRT
<213> Homo sapiens

<400> 166
Met Leu Ser Arg Arg Leu His Cys Leu Val Leu Tyr Phe Leu Leu Leu
1 5 10 15

Leu Leu Ser Phe Ile His Thr Leu Ser Val Ser His Ile Cys Ser Ser
20 25 30

Phe Ile Trp Leu Phe Pro Lys Asn Ile Glu Ser Glu Ala Thr Met
35 40 45

<210> 167
<211> 45
<212> PRT
<213> Homo sapiens

<400> 167
Met Glu Lys Met Gly Gln Gly Leu Leu Ser Ser Thr Tyr Leu Thr Val
1 5 10 15

Leu His Leu Ile Gln Leu Val Gly Cys Gly Leu Leu Thr Glu Glu Ile
20 25 30

Lys Glu Ser Lys Tyr Leu Ile Lys Thr Leu Gly Ser Gly
35 40 45

<210> 168
<211> 207
<212> PRT
<213> Homo sapiens

<400> 168
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Leu
35 40 45

Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe Asn Pro Lys Phe
50 55 60

Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr Lys Lys Ser Gly
65 70 75 80

Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys Leu Glu Gln Asp
85 90 95

Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln Gly Asn Leu Thr
100 105 110

Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys
115 120 125

Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu Ala Val Ala Ser
130 135 140

Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly Thr Gln Ser Ala
145 150 155 160

His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val Ser Asp Ser Ser
165 170 175

Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr Gln Ser Arg Gly
180 185 190

Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg Val Lys Asp
195 200 205

<210> 169
<211> 50
<212> PRT
<213> Homo sapiens

<400> 169
Met Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val
1 5 10 15

Val Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro
20 25 30

Thr Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile
35 40 45

Val Gln
50

<210> 170
<211> 42
<212> PRT
<213> Homo sapiens

<400> 170
Met Ala His Pro Gly Leu Pro Lys Thr Val Pro Val Tyr Ala Val Val
1 5 10 15

Leu Ala Leu Leu Ile Met Thr Leu Pro Leu Thr Leu Thr Ile Asn Leu
20 25 30

Asp Asp Asn Leu Tyr Gly Asn Ser Ala Lys
35 40

<210> 171
<211> 55
<212> PRT
<213> Homo sapiens

<400> 171
Met Arg Pro Trp Trp Ser Leu Leu Leu Glu Ala Cys Ala Thr Cys Ala
1 5 10 15

Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys Thr Gln Glu Val Ser His
20 25 30

Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met Arg Arg Arg Cys Cys Leu
35 40 45

Pro Ser Pro Arg Ser Cys Thr
50 55

<210> 172
<211> 108
<212> PRT
<213> Homo sapiens

<400> 172
Met Ala Leu Ala Gly Ser Val Phe Val Leu Gly Gly Val Leu Val Leu
1 5 10 15

Cys Val Glu Arg Asn Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu
20 25 30

```
Pro Lys Ser Gln Pro Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser
         35                  40                  45

Phe Glu Arg Ser Trp Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met
     50                  55                  60

Val Thr Cys Arg Gln Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg
 65                  70                  75                  80

Gly Gly Gly Pro Lys Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly
                 85                  90                  95

Ala Cys Ala Val Arg Pro Glu Ile Gln Trp Glu Val
            100                 105
```

<210> 173
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 173

```
Met Phe Leu Phe Phe Tyr Leu Ser Leu Ala Val Tyr Ala Gln Arg Gln
  1               5                  10                  15

Xaa Ser Gly Ser Cys Arg Gln Thr Asp His Arg Trp Lys Ser Arg Gly
            20                  25                  30

Ala Arg Arg Cys Phe Leu Glu Pro Arg Asp Pro Gly Ser Val Pro Gly
         35                  40                  45

His Pro
     50
```

<210> 174
<211> 566
<212> PRT
<213> Homo sapiens

<400> 174

```
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
  1               5                  10                  15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
            20                  25                  30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
         35                  40                  45

Val Thr Trp Gly Leu Asn Arg Thr Leu Lys Pro Gln Arg Val Ile Val
     50                  55                  60
```

```
Val Gly Ala Gly Val Ala Gly Leu Val Ala Ala Lys Val Leu Ser Asp
 65                  70                  75                  80

Ala Gly His Lys Val Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly
                 85                  90                  95

Arg Ile Phe Thr Tyr Arg Asp Gln Asn Thr Gly Trp Ile Gly Glu Leu
            100                 105                 110

Gly Ala Met Arg Met Pro Ser Ser His Arg Ile Leu His Lys Leu Cys
        115                 120                 125

Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn
    130                 135                 140

Thr Trp Thr Glu Val His Glu Val Lys Leu Arg Asn Tyr Val Val Glu
145                 150                 155                 160

Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly
                165                 170                 175

His Ser Pro Glu Asp Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys
            180                 185                 190

Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg
        195                 200                 205

His Thr Leu Leu Glu Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro
    210                 215                 220

Ala Val Gln Leu Leu Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr
225                 230                 235                 240

Leu Ser Phe Ala Glu Ala Leu Arg Ala His Ser Cys Leu Ser Asp Arg
                245                 250                 255

Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala
            260                 265                 270

Leu Leu Ser Ser Leu Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val
        275                 280                 285

Ala Met Thr Gln Gly Pro His Asp Val His Val Gln Ile Glu Thr Ser
    290                 295                 300

Pro Pro Ala Arg Asn Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu
305                 310                 315                 320

Thr Ala Ser Gly Pro Ala Val Lys Arg Ile Thr Phe Ser Pro Pro Leu
                325                 330                 335

Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro Ala
            340                 345                 350

Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu His
        355                 360                 365

Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile Phe
    370                 375                 380
```

```
Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr Trp
385                 390                 395                 400

Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala Leu
                405                 410                 415

Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val Arg
            420                 425                 430

Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp Gln
        435                 440                 445

His Ser Gln Gly Gly Phe Val Val Gln Pro Pro Ala Leu Trp Gln Thr
    450                 455                 460

Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala Gly
465                 470                 475                 480

Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys Leu
                485                 490                 495

Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala Ser Asp
            500                 505                 510

Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln Gly His
        515                 520                 525

Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys Glu Glu
    530                 535                 540

Gly Ser His Pro Pro Val Gln Gly Gln Leu Ser Leu Gln Asn Thr Thr
545                 550                 555                 560

His Thr Arg Thr Ser His
                565
```

<210> 175
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (76)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 175

```
Met Ala Arg Ala Arg Gly Ser Pro Cys Pro Pro Leu Pro Pro Gly Arg
  1               5                  10                  15

Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
             20                  25                  30

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
         35                  40                  45

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
```

50 55 60

Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Xaa Leu Ala Glu Val
65 70 75 80

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
85 90 95

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
100 105 110

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
115 120 125

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
130 135 140

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
145 150 155 160

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
165 170 175

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
180 185 190

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
195 200 205

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
210 215 220

<210> 176
<211> 123
<212> PRT
<213> Homo sapiens

<400> 176
Met His Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys Pro Ser
1 5 10 15

Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Val His Leu Asn Ile
20 25 30

Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr
35 40 45

Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe Gln Tyr
50 55 60

Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly Leu Thr
65 70 75 80

Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe Asp Ser
85 90 95

```
Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg Ala Ala
            100                 105                 110

Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
        115                 120
```

<210> 177
<211> 59
<212> PRT
<213> Homo sapiens

<400> 177

```
Met Gly Leu Ser Val Leu Leu Pro Leu Cys Leu Leu Gly Pro Gly Arg
  1               5                  10                  15

Phe Thr Ser Gly Gln Lys Pro Leu Asp Thr Pro Gly Leu Gly Ala Ala
            20                  25                  30

Val Leu Ser Val Arg Lys Ala Gly Leu Lys Met Arg Ser His Leu Thr
        35                  40                  45

Pro Ser Val Cys Thr Val Pro Ser Pro Gly Ser
    50                  55
```

<210> 178
<211> 105
<212> PRT
<213> Homo sapiens

<400> 178

```
Met Asp Thr Val Phe Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arg
  1               5                  10                  15

Ile Val Phe Met Leu Gly Phe Val Val Val Leu Ser Phe Leu Leu Gly
            20                  25                  30

Gly Tyr Leu Leu Phe Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr
        35                  40                  45

Asn Glu Trp Tyr Arg Gly Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu
    50                  55                  60

Val Ala Trp Pro Pro Ser Ala Glu Pro Gln Val His Arg Asn Ile His
65                  70                  75                  80

Ser His Gly Leu Arg Ser Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe
                85                  90                  95

Pro Cys His Glu Arg Lys Lys Gln Glu
            100                 105
```

<210> 179

<211> 87
<212> PRT
<213> Homo sapiens

<400> 179
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
35 40 45

Pro Val Glu Ala Pro Cys Leu Glu Val Val Phe Lys Gln Lys Asn Gly
50 55 60

Lys Asp Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
65 70 75 80

Ser Leu Leu Gly Pro Phe Ile
85

<210> 180
<211> 87
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (55)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (66)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 180
Met Ala Asp Pro His Val Ser Phe Leu Ser Phe Arg Gln Leu Phe Ser
1 5 10 15

Trp Ala Ala Val Ile Leu Leu Arg Gly Ile Leu Gly Thr Val Ala Pro
20 25 30

Pro Pro Cys Pro Cys Val Leu Asp Leu Ala Val Tyr Pro Leu His Leu
35 40 45

Pro Val Glu Ala Pro Cys Xaa Glu Val Val Phe Lys Gln Lys Asn Gly
50 55 60

Lys Xaa Asn Cys Leu Val Phe Tyr Pro Asp Pro Ile Pro Leu Arg Gly
65 70 75 80

Ser Leu Leu Gly Pro Phe Ile
85

<210> 181
<211> 49
<212> PRT
<213> Homo sapiens

<400> 181
Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys
1 5 10 15

Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
20 25 30

Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
35 40 45

Met

<210> 182
<211> 23
<212> PRT
<213> Homo sapiens

<400> 182
Leu Gly Ser Leu Ser Thr Ala Pro Ser Ser Ala Leu Pro Thr Leu Gly
1 5 10 15

Ala Arg Arg Thr Arg Ser Lys
20

<210> 183
<211> 103
<212> PRT
<213> Homo sapiens

<400> 183
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
50 55 60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
65 70 75 80

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
85 90 95

Thr Arg Val Leu Phe Ile Tyr

100

<210> 184
<211> 198
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 184
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp
65 70 75 80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
180 185 190

Arg Val Leu Phe Ile Tyr
195

<210> 185
<211> 70
<212> PRT
<213> Homo sapiens

<400> 185
Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
1 5 10 15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
20 25 30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
35 40 45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
50 55 60

Arg Val Leu Phe Ile Tyr
65 70

<210> 186
<211> 82
<212> PRT
<213> Homo sapiens

<400> 186
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
50 55 60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
65 70 75 80

Leu Leu

<210> 187
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 187
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr

120

20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
35 40 45

<210> 188
<211> 33
<212> PRT
<213> Homo sapiens

<400> 188
Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
20 25 30

Ser

<210> 189
<211> 231
<212> PRT
<213> Homo sapiens

<400> 189
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
1 5 10 15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
20 25 30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
35 40 45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
50 55 60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
65 70 75 80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
85 90 95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
100 105 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
115 120 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
130 135 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
145 150 155 160

```
Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
                165                 170                 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
            180                 185                 190

Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
        195                 200                 205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
    210                 215                 220

Gly Phe Ile Leu Ile Pro Cys
225                 230
```

<210> 190
<211> 612
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (245)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (246)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (249)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 190

```
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85                  90                  95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
```

```
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145                 150                 155                 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165                 170                 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180                 185                 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195                 200                 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210                 215                 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Xaa Xaa Ser Thr Xaa Leu Glu Lys Pro Gln Asn Met
                245                 250                 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385                 390                 395                 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
                405                 410                 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
            420                 425                 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
```

```
        435                 440                 445

Cys Ser Asn Asp Cys Pro Arg Lys Ile Thr Pro Phe Gly Val Asn Gln
    450                 455                 460

Pro Gly Pro Tyr Ile Met Tyr Thr Thr Val Asp Ala Asn Gly Tyr Leu
465                 470                 475                 480

Lys Asn Gly Ser Ala Gly Gln Leu Ser Gln Ser Ala His Leu Ala Leu
                485                 490                 495

Gln Leu Pro Tyr Asn Val Leu Gly Leu Gly Arg Ser Ala Asn Phe Leu
            500                 505                 510

Asp His Leu Tyr Val Gly Ile Pro Arg Pro Ser Gly Glu Lys Ser Ile
        515                 520                 525

Arg Lys Gln Glu Trp Thr Ala Ile Ile Pro Asn Ser Gln Leu Ile Val
    530                 535                 540

Ile Pro Tyr Pro His Asn Val Pro Arg Ser Trp Ser Ala Lys Leu Tyr
545                 550                 555                 560

Leu Thr Pro Ser Asn Ile Val Leu Leu Thr Ala Ile Ala Leu Ile Gly
                565                 570                 575

Val Cys Val Phe Ile Leu Ala Ile Ile Gly Ile Leu His Trp Gln Glu
            580                 585                 590

Lys Lys Ala Asp Asp Arg Glu Lys Arg Gln Glu Ala His Arg Phe His
        595                 600                 605

Phe Asp Ala Met
    610
```

<210> 191
<211> 456
<212> PRT
<213> Homo sapiens

<400> 191

```
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85                  90                  95
```

```
Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145                 150                 155                 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165                 170                 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180                 185                 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195                 200                 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210                 215                 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
                245                 250                 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385                 390                 395                 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
                405                 410                 415
```

```
Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
            420                 425                 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
        435                 440                 445

Cys Ser Asn Asp Cys Pro Arg Arg
    450                 455
```

<210> 192
<211> 184
<212> PRT
<213> Homo sapiens

<400> 192

```
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
  1               5                  10                  15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
             20                  25                  30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
         35                  40                  45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
     50                  55                  60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
 65                  70                  75                  80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
                 85                  90                  95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
            100                 105                 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
        115                 120                 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
    130                 135                 140

Thr Leu Lys Gly Asn Ser Trp Asn Cys Ser Arg Ser Pro His Leu Leu
145                 150                 155                 160

Leu Tyr Thr Leu Val Arg Arg Gly Thr Asp Trp Ile Ser Tyr Phe Pro
                165                 170                 175

Arg Gly Ser Gln Pro Asp Asn Gln
            180
```

<210> 193
<211> 146
<212> PRT
<213> Homo sapiens

<400> 193
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Leu Asp
50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp
85 90 95

Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
100 105 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
115 120 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
130 135 140

Gly Leu
145

<210> 194
<211> 124
<212> PRT
<213> Homo sapiens

<400> 194
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
1 5 10 15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
20 25 30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
35 40 45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
50 55 60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
65 70 75 80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
85 90 95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
100 105 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp
115 120

<210> 195
<211> 51
<212> PRT
<213> Homo sapiens

<400> 195
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
35 40 45

Leu Leu Ala
50

<210> 196
<211> 319
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 196
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met

65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu
85 90 95

Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val
100 105 110

His Glu Xaa Lys Leu Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys
115 120 125

Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp
130 135 140

Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu
145 150 155 160

Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu
165 170 175

Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu
180 185 190

Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu
195 200 205

Ala Leu Arg Ala Xaa Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg
210 215 220

Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu
225 230 235 240

Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly
245 250 255

Pro His Asp Val His Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn
260 265 270

Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro
275 280 285

Ala Val Lys Arg Ile Thr Phe Ser Pro Arg Cys Pro Ala Thr Cys Arg
290 295 300

Arg Arg Cys Gly Gly Cys Thr Thr Cys Arg Pro Pro Arg Cys Ser
305 310 315

<210> 197
<211> 130
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (38)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 197
Pro Phe Cys Ser Gly Phe Phe Pro Ser Leu Trp Ile Tyr Leu Pro Phe
1 5 10 15

Ile Phe Asn Val Ser Asp Leu Trp Met Gly Ser Leu Ser Gly Cys Ala
20 25 30

Leu Pro Phe Cys Leu Xaa Val Phe Phe Leu Thr Val Ser Pro Ser Ala
35 40 45

Val Gly Leu Leu Xaa Phe Ala Gly Gly Pro Leu Gln Thr Leu Phe Ala
50 55 60

Trp Val Ser Pro Val Glu Ala Ala Glu Gln Gln Arg Leu Leu Pro Val
65 70 75 80

Leu Ser Ser Gly Ser Phe Val Ser Glu Gly Thr Cys Gln Met Pro Ala
85 90 95

Arg Ala Leu Leu Tyr Glu Val Ser Val Gly Pro Tyr Trp Glu Ile Pro
100 105 110

Pro Ser Gln Asp Thr Arg Arg Ser Gly Thr Tyr Leu Arg Arg Gln Ser
115 120 125

Asp Pro
130

<210> 198
<211> 108
<212> PRT
<213> Homo sapiens

<400> 198
His Glu Gly Ser Cys Arg Ala Pro Gly Phe Ser Ala His Lys Gly Arg
1 5 10 15

Gly Cys Pro Ser Pro Arg Met Thr Leu Pro Ser Arg Ala Leu Ala Ser
20 25 30

Leu Gly Val Gly Val Trp Gly Met Leu Arg Leu Asn Gln Val Thr Val
35 40 45

Ser Cys Gly Gly Ser Arg Trp Ser Ser Arg Val Ala Leu Gly Ala Phe
50 55 60

Ser Trp Val Cys Gly Val Ala Leu Val Leu Gln Pro Ser Gly Gly Gly
65 70 75 80

Leu Gly Leu Thr Ser Pro Ser Glu Gly Cys Trp Glu Gly Glu Leu Ala
85 90 95

Leu Ala Val Leu Arg Ala Pro Gly Gly Ser Pro Ser
100 105

<210> 199
<211> 104
<212> PRT
<213> Homo sapiens

<400> 199
Ile Pro Leu Thr Leu Pro Gly Ile Phe Leu Leu Ile Arg Leu Phe Trp
1 5 10 15

Arg Leu Gly Gln Ser Ile Cys Gly Pro Gly Lys Leu Val Leu Trp Pro
20 25 30

Gln Phe Cys Cys Gly Cys Ala Val Ile Ser Gly His Cys Val Pro Arg
35 40 45

Gly Met Pro Ser Ser Trp Leu Pro Gly Cys Phe Val Leu Leu Cys Leu
50 55 60

Val Ala Val Gly Cys Gln Leu Arg Glu Trp Gly Val Gly Gly Val Ser
65 70 75 80

Ala Val Gly Leu Leu Ala Leu Pro His Leu Gln Val Leu Gly Met Arg
85 90 95

Gly Arg Gly Leu Ile Ser Gly Gly
100

<210> 200
<211> 237
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (142)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 200
Gly Pro Ala Gly Lys Glu Ala Trp Ile Trp Ser Trp Leu Leu Pro Ser
1 5 10 15

Pro Gly Pro Ala Pro Leu Pro Ser Ala Ser Trp Gly Leu Cys Gly Asp
20 25 30

Ala Pro Arg Ala Ala Ala Arg Gly Pro Val Glu Pro Gly Ala Ala Arg
35 40 45

Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu Leu Met
50 55 60

Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp Trp Arg
65 70 75 80

Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile Asp Thr Tyr
85 90 95

```
Leu Asn Ala Ala Leu Asp Leu Leu Gly Gly Glu Asp Gly Leu Cys Gln
            100                 105                 110

Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro Arg Tyr Gly Tyr Lys
        115                 120                 125

Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro Leu Phe Gly Xaa His Leu
    130                 135                 140

Asn Ile Gly Ile Pro Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg
145                 150                 155                 160

Cys Tyr Glu Thr Cys Gly Lys Ser Lys Asn Asp Cys Asp Glu Glu Phe
                165                 170                 175

Gln Tyr Cys Leu Ser Lys Ile Cys Arg Asp Val Gln Lys Thr Leu Gly
            180                 185                 190

Leu Thr Gln His Val Gln Ala Cys Glu Thr Thr Val Glu Leu Leu Phe
        195                 200                 205

Asp Ser Val Ile His Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg
    210                 215                 220

Ala Ala Cys Arg Cys His Tyr Glu Glu Lys Thr Asp Leu
225                 230                 235
```

<210> 201
<211> 8
<212> PRT
<213> Homo sapiens

<400> 201
Cys Cys Asn Gln His Asp Arg Cys
1 5

<210> 202
<211> 15
<212> PRT
<213> Homo sapiens

<400> 202
Ser Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr
1 5 10 15

<210> 203
<211> 16
<212> PRT
<213> Homo sapiens

<400> 203
Leu Thr Lys Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr Cys Gly
1 5 10 15

<210> 204
<211> 260
<212> PRT
<213> Homo sapiens

<400> 204
Gly Thr Ser Ser Ala Arg Pro Arg Gly Ala Leu Pro Gly Gly Ser Ala
1 5 10 15

Pro Ser Ala Pro His Gly Gln Leu Pro Gly Arg Ala Gln Pro Ala Pro
20 25 30

Val Ser Gly Pro Pro Pro Thr Ser Gly Leu Cys His Phe Asp Pro Ala
35 40 45

Ala Pro Trp Pro Leu Trp Pro Gly Pro Trp Gln Leu Pro Pro His Pro
50 55 60

Gln Asp Trp Pro Ala His Pro Asp Ile Pro Gln Asp Trp Val Ser Phe
65 70 75 80

Leu Arg Ser Phe Gly Gln Leu Thr Leu Cys Pro Arg Asn Gly Thr Val
85 90 95

Thr Gly Lys Trp Arg Gly Ser His Val Val Gly Leu Leu Thr Thr Leu
100 105 110

Asn Phe Gly Asp Gly Pro Asp Arg Asn Lys Thr Arg Thr Phe Gln Ala
115 120 125

Thr Val Leu Gly Ser Gln Met Gly Leu Lys Gly Ser Ser Ala Gly Gln
130 135 140

Leu Val Leu Ile Thr Ala Arg Val Thr Thr Glu Arg Thr Ala Gly Thr
145 150 155 160

Cys Leu Tyr Phe Ser Ala Val Pro Gly Ile Leu Pro Ser Ser Gln Pro
165 170 175

Pro Ile Ser Cys Ser Glu Glu Gly Ala Gly Asn Ala Thr Leu Ser Pro
180 185 190

Arg Met Gly Glu Glu Cys Val Ser Val Trp Ser His Glu Gly Leu Val
195 200 205

Leu Thr Lys Leu Leu Thr Ser Glu Glu Leu Ala Leu Cys Gly Ser Arg
210 215 220

Leu Leu Val Leu Gly Ser Phe Leu Leu Leu Phe Cys Gly Leu Leu Cys
225 230 235 240

Cys Val Thr Ala Met Cys Phe His Pro Arg Arg Glu Ser His Trp Ser
245 250 255

Arg Thr Arg Leu
260

<210> 205
<211> 80
<212> PRT
<213> Homo sapiens

<400> 205
Ala Arg Ala Pro Pro Gly Pro Glu Gly Leu Ser Pro Glu Ala Gln Pro
1 5 10 15

Pro Leu Leu Pro Met Gly Asn Cys Gln Ala Gly His Asn Leu His Leu
20 25 30

Cys Leu Ala His His Pro Pro Leu Val Cys Ala Thr Leu Ile Leu Leu
35 40 45

Leu Leu Gly Leu Ser Gly Leu Gly Leu Gly Ser Phe Leu Leu Thr His
50 55 60

Arg Thr Gly Leu Arg Thr Leu Thr Ser Pro Arg Thr Gly Ser Leu Phe
65 70 75 80

<210> 206
<211> 224
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (9)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (143)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (186)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 206
Arg Phe Leu Ser Val Xaa Pro Gln Xaa Glu Val Pro Phe Leu Leu His
1 5 10 15

Pro Cys Val Cys Phe Xaa Gly Gly His Pro Ser Leu Leu Pro Asp Pro
20 25 30

Cys Arg Ala Val Gly Gly Gly Trp Glu Ala Pro Arg Cys Cys Leu His
35 40 45

Glu Ala Leu Cys Gln Ser Leu Gly Cys Lys Ala Glu Glu Ile Val Ser
50 55 60

Val Ser Glu Ser Ser Ser Ala Gln Arg Cys Trp Tyr Leu Leu Arg Gly
65 70 75 80

Arg Lys Ala Gly Gly Arg Gly Pro Ala Ser Pro Val Leu Phe Ala Leu
85 90 95

Met Arg Leu Glu Ser Leu Cys His Leu Cys Leu Ala Cys Leu Phe Phe
100 105 110

Arg Leu Pro Ala Thr Arg Thr Val Tyr Cys Met Asn Glu Ala Glu Ile
115 120 125

Val Asp Val Ala Leu Gly Ile Leu Ile Glu Ser Arg Lys Gln Xaa Lys
130 135 140

Ala Cys Glu Gln Pro Ala Leu Ala Gly Ala Asp Asn Pro Glu His Ser
145 150 155 160

Pro Pro Cys Ser Val Ser Pro His Thr Ser Ser Gly Ser Ser Ser Glu
165 170 175

Glu Glu Asp Ser Gly Lys Gln Ala Leu Xaa Pro Gly Leu Ser Pro Ser
180 185 190

Gln Arg Pro Gly Gly Ser Ser Ser Ala Cys Ser Arg Ser Pro Glu Glu
195 200 205

Glu Glu Glu Glu Asp Val Leu Lys Tyr Val Arg Glu Ile Phe Phe Ser
210 215 220

<210> 207
<211> 199
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
<222> (103)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (191)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 207
Val Pro Gly Trp Pro Arg Ala Cys Ser Pro Cys Gln Ala Asp Ser Pro
1 5 10 15

Arg Ala His Pro Pro Lys Leu Arg Gly Ile Leu Arg Trp Ala Pro Val
20 25 30

Pro Leu Xaa Cys Ala Ala Leu Cys Pro Pro Leu Asp Ser Gly Met Ser
35 40 45

Met Ala Ala Cys Pro Glu Ala Pro Glu Pro Ser Phe Leu Arg Glu Val
50 55 60

Pro Ser Ser Pro Ala Ser Thr Gln Trp His Arg Pro Cys Asn Phe Arg
65 70 75 80

Gln Val Glu Ala Asn Pro Arg Lys Glu Pro Lys Asn Leu Val Trp Arg
85 90 95

Asp Val Ser Leu Gly Gln Xaa Ser Arg Thr Pro Arg Gly Ser Gly Leu
100 105 110

Glu Leu Val Arg Val Cys Gly Gly Gly Met Gln Arg Asp Lys Thr Val
115 120 125

Val Glu Glu Arg Val Gly Glu Glu Arg Glu Arg Glu Arg Glu Arg Glu
130 135 140

Ser Leu Gly Gly Ala Gly Lys His Gly Glu Met Arg Cys Val Tyr Val
145 150 155 160

Arg Glu Ser Val Gly Ala Pro Gly Arg Ala Gly Gly Gly Gly Asn Gly
165 170 175

Val Asn Ser Val Gly Cys Val Arg Thr Val His Ser Gly Ser Xaa Pro
180 185 190

Pro Pro Ser Ala Gly Val Ser
195

<210> 208
<211> 174
<212> PRT
<213> Homo sapiens

<400> 208
Thr Arg Pro Gly Lys Glu Leu Asn Leu Val Phe Gly Leu Gln Leu Ser
1 5 10 15

Met Ala Arg Ile Gly Ser Thr Val Asn Met Asn Leu Met Gly Trp Leu
20 25 30

Tyr Ser Lys Ile Glu Ala Leu Leu Gly Ser Ala Gly His Thr Thr Leu
35 40 45

Gly Ile Thr Leu Met Ile Gly Gly Ile Thr Cys Ile Leu Ser Leu Ile
50 55 60

Cys Ala Leu Ala Leu Ala Tyr Leu Asp Gln Arg Ala Glu Arg Ile Leu
65 70 75 80

His Lys Glu Gln Gly Lys Thr Gly Glu Val Ile Lys Leu Thr Asp Val
85 90 95

Lys Asp Phe Ser Leu Pro Leu Trp Leu Ile Phe Ile Ile Cys Val Cys
100 105 110

Tyr Tyr Val Ala Val Phe Pro Phe Ile Gly Leu Gly Lys Val Phe Phe
115 120 125

Thr Glu Lys Phe Gly Phe Ser Ser Gln Ala Ala Ser Ala Ile Asn Ser
130 135 140

Val Val Tyr Val Ile Ser Ala Pro Met Ser Pro Val Phe Gly Leu Leu
145 150 155 160

Val Asp Lys Thr Gly Lys Asn Ile Ile Trp Val Leu Cys Ala
165 170

<210> 209
<211> 31
<212> PRT
<213> Homo sapiens

<400> 209
Cys Lys Asp Leu Cys Ser Arg Val Tyr Leu Leu Thr Leu Ser Pro Leu
1 5 10 15

Leu Ser Tyr Asp Pro Ala Thr Ser His Ser Pro Arg Asn Thr Gln
20 25 30

<210> 210
<211> 369
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (78)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 210
Ile Ile Cys Glu Cys Trp Glu Glu Glu Cys Gln Ser Cys Arg Leu Lys
1 5 10 15

```
Ile Thr Gln Pro Arg Glu Ile Cys Arg Met Asp Phe Leu Val Leu Phe
            20                  25                  30

Leu Phe Tyr Leu Ala Ser Val Leu Met Gly Leu Val Leu Ile Cys Val
        35                  40                  45

Cys Ser Lys Thr His Ser Leu Lys Gly Leu Ala Arg Gly Gly Ala Gln
    50                  55                  60

Ile Phe Ser Cys Ile Ile Pro Glu Cys Leu Gln Arg Ala Xaa His Gly
65                  70                  75                  80

Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe Ile Val Leu
                85                  90                  95

His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr Trp Glu Val
            100                 105                 110

Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr Leu Leu Leu
        115                 120                 125

Pro Tyr Leu Leu Leu Gly Val Asn Leu Phe Phe Phe Thr Leu Thr Cys
    130                 135                 140

Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu Leu Phe Leu
145                 150                 155                 160

His Val Tyr Glu Phe Asp Glu Val Met Phe Pro Lys Asn Val Arg Cys
                165                 170                 175

Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Lys His Cys Ser Val
            180                 185                 190

Cys Asn Trp Cys Val His Arg Phe Asp His His Cys Val Trp Val Asn
        195                 200                 205

Asn Cys Ile Gly Ala Trp Asn Ile Arg Tyr Phe Leu Ile Tyr Val Leu
    210                 215                 220

Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser Thr Thr Phe
225                 230                 235                 240

Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu Thr Tyr Ile
                245                 250                 255

Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe Leu Ile Gln
            260                 265                 270

Tyr Leu Phe Leu Thr Phe Pro Arg Ile Val Phe Met Leu Gly Phe Val
        275                 280                 285

Val Val Leu Ser Phe Leu Leu Gly Gly Tyr Leu Leu Phe Val Leu Tyr
    290                 295                 300

Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg Gly Asp Trp
305                 310                 315                 320

Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro Ser Ala Glu
                325                 330                 335
```

```
Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg Ser Asn Leu
            340                 345                 350

Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg Lys Lys Gln
        355                 360                 365

Glu
```

<210> 211
<211> 147
<212> PRT
<213> Homo sapiens

<400> 211

```
Leu Leu Ser Phe Lys Ile Arg Gly Leu Arg Thr Glu Asp Ala Gly Trp
  1               5                  10                  15

Ala Gln Ser Ser Ser Gly Gly Leu Cys Val Arg Gly Asp Ala Phe Trp
             20                  25                  30

Met Pro Ser Ser Ser Ser Gly Leu Gly Ser Pro Ser Arg Pro Pro Ser
         35                  40                  45

Ser Phe Leu Cys Leu Leu Leu Leu Leu Leu Pro Pro Ala Ala Leu Ala
     50                  55                  60

Leu Leu Leu Phe Phe Leu Asp Phe Phe Pro Pro Arg Ala Ala Val Ser
 65                  70                  75                  80

Pro Phe Leu Pro Asp His Cys Ser Ala Arg Gln Pro Arg Val Trp Arg
                85                  90                  95

Arg Glu Thr Leu Asn Arg Ser Ala Ser Gly Leu Gly Cys Trp Ala Arg
            100                 105                 110

Ser Thr Glu Gln Gly Ala Val Gly Val Ala Thr Gly Thr Val Leu Asp
        115                 120                 125

Ile Ser Leu Pro Ala Ser Cys Leu Ser Leu Trp Pro Pro Gly Pro Ser
    130                 135                 140

Gly Gly Ile
145
```

<210> 212
<211> 143
<212> PRT
<213> Homo sapiens

<400> 212

```
Gln Leu Gly Leu Cys Leu Thr Ser Ala Ser Leu Pro Pro Ala Ser Arg
  1               5                  10                  15

Cys Gly His Gln Ala Pro Leu Gly Ala Ser Asp Leu Ser Ala His His
             20                  25                  30
```

```
Ser Ala Pro Gly Phe Ser Asp Ser Tyr Phe Thr Met Ser Cys Gln Ser
         35                  40                  45

Ser Leu Ser Arg Ala Glu Ile Leu Gln Cys Pro Leu Val Pro Ser Val
     50                  55                  60

Ser Pro Pro Thr His Leu Pro Gln Gly Arg Ala Asn Lys Ser Ser Arg
 65                  70                  75                  80

Ala Ser Leu Pro Leu Leu Pro Gln Thr His Trp Cys Leu Phe Pro Ser
                 85                  90                  95

Ala Arg Gly Trp Arg Arg Gly Ile Gln Ser Gly Leu Pro Pro Gly Gly
            100                 105                 110

Ser Cys Thr Ser Pro Arg Ser Pro Pro Gln Thr Leu His Gln His Ile
        115                 120                 125

Thr Leu Val Asn His Asn Thr Ser Tyr Trp Gln Ser Pro Ser Thr
    130                 135                 140
```

<210> 213
<211> 160
<212> PRT
<213> Homo sapiens

<400> 213

```
His Gln Pro Pro Cys Leu Leu Pro Leu Ala Val Ala Thr Arg Pro Leu
  1               5                  10                  15

Trp Gly His Leu Thr Cys Leu Pro Ile Ile Leu His Leu Val Ser Val
             20                  25                  30

Thr Leu Thr Ser Pro Cys Leu Ala Asn Gln Ala Phe Gln Gly Gln Arg
         35                  40                  45

Ser Tyr Asn Ala Leu Trp Cys Pro Leu Phe Leu Leu Leu Pro Thr Ser
     50                  55                  60

Pro Lys Gly Glu Gln Thr Asn His Pro Glu Pro Ala Cys Pro Cys Phe
 65                  70                  75                  80

Pro Lys Leu Thr Gly Val Phe Ser Leu Gln His Val Val Gly Ala Glu
                 85                  90                  95

Glu Phe Ser Gln Val Phe Leu Leu Val Asp Pro Val Pro Val Leu Asp
            100                 105                 110

His Leu Leu Lys Leu Phe Thr Ser Thr Ser His Leu Leu Ile Ile Ile
        115                 120                 125

Pro His Ile Gly Lys Ala Pro Ala Pro Asp Ser Leu Leu Glu Glu Leu
    130                 135                 140

Ser Leu Ser Leu Ala Thr His Cys Lys Val Ala Val Ala Arg Phe Thr
145                 150                 155                 160
```

<210> 214
<211> 157
<212> PRT
<213> Homo sapiens

<400> 214
Met Ala Ala Glu Gly Ser Arg Phe Ser Ser Gln Ser Pro Gly Leu Val
1 5 10 15

Asp Arg Gln Gly Pro Lys Cys Asp Pro Ser Arg Leu Val Ser Pro Trp
20 25 30

Gly Arg His Gly Leu Arg Ile Leu Gln Ile Gly His His His Gly Arg
35 40 45

Asp Gly Gln His Glu Ala Thr His His Leu Leu Arg Val Leu Arg Ala
50 55 60

Pro Arg Val Gly Lys Ala Asp Glu Gly Ala Val Asp Ser Asp Pro Ser
65 70 75 80

Thr Pro Leu Gln Leu Lys His Glu Ala Ala His Ala Glu Asp His Ala
85 90 95

Gln Gln Val His Val Val Arg Arg Arg Val Val Gln Gly Arg Val Thr
100 105 110

Phe Ala Arg Arg Gly Leu Val Pro Gln His Phe Val Arg Pro Pro Trp
115 120 125

Val Arg His Ile Val Ser Gly His Ser Glu Ser Lys Ala Arg Ser Arg
130 135 140

Leu Phe Arg Cys Arg Asn Arg Ser Phe Arg Arg Ala Ser
145 150 155

<210> 215
<211> 38
<212> PRT
<213> Homo sapiens

<400> 215
Arg Leu Val Ser Pro Trp Gly Arg His Gly Leu Arg Ile Leu Gln Ile
1 5 10 15

Gly His His His Gly Arg Asp Gly Gln His Glu Ala Thr His His Leu
20 25 30

Leu Arg Val Leu Arg Ala
35

<210> 216
<211> 12
<212> PRT
<213> Homo sapiens

<400> 216
Pro Thr Asp Val Leu Lys Ile Arg Met Gln Ala Gln
1 5 10

<210> 217
<211> 7
<212> PRT
<213> Homo sapiens

<400> 217
Thr Tyr Glu Gln Leu Lys Arg
1 5

<210> 218
<211> 137
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (33)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (71)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 218
Arg Pro Arg Pro Ser Ala Ser Ser Leu Ala Arg Ser Ala Ser Leu Leu
1 5 10 15

Pro Ala Ala His Gly Xaa Gly Val Gly Gly Ala Gly Gly Gly Ser Ser
20 25 30

Xaa Leu Arg Ser Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly
35 40 45

Glu Pro Glu Gln Ala Ala Gly Asp Ala Pro Pro Pro Tyr Ser Ser Ile
50 55 60

Ser Ala Glu Ser Ala His Xaa Phe Asp Tyr Lys Asp Glu Ser Gly Phe
65 70 75 80

Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr Thr Leu Pro Ser Tyr Asp
85 90 95

```
Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr Ile Pro Leu Val Pro Gly
            100                 105                 110

Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala Asp Gln
        115                 120                 125

Leu Arg Ile Gly Asn Asp Gly Ile Phe
    130                 135
```

<210> 219
<211> 20
<212> PRT
<213> Homo sapiens

<400> 219
```
Arg Tyr Gln Gln Leu Gln Asn Glu Glu Glu Ser Gly Glu Pro Glu Gln
  1               5                  10                  15

Ala Ala Gly Asp
             20
```

<210> 220
<211> 22
<212> PRT
<213> Homo sapiens

<400> 220
```
Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp Phe Asp Asp Ala
  1               5                  10                  15

Asp Gln Leu Arg Ile Gly
             20
```

<210> 221
<211> 103
<212> PRT
<213> Homo sapiens

<400> 221
```
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
  1               5                  10                  15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
            20                  25                  30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
        35                  40                  45

Ser Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp
    50                  55                  60

Val Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn
65                  70                  75                  80
```

Tyr Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg
85 90 95

Thr Arg Val Leu Phe Ile Tyr
100

<210> 222
<211> 198
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 222
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln His Xaa Phe Asp Tyr
20 25 30

Lys Asp Glu Ser Gly Phe Pro Lys Pro Pro Ser Tyr Asn Val Ala Thr
35 40 45

Thr Leu Pro Ser Tyr Asp Glu Ala Glu Arg Thr Lys Ala Glu Ala Thr
50 55 60

Ile Pro Leu Val Pro Gly Arg Asp Glu Asp Phe Val Gly Arg Asp Asp
65 70 75 80

Phe Asp Asp Ala Asp Gln Leu Arg Ile Gly Asn Asp Gly Ile Phe Met
85 90 95

Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe Leu
100 105 110

Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile Ser
115 120 125

Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe Ser
130 135 140

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
145 150 155 160

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
165 170 175

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
180 185 190

Arg Val Leu Phe Ile Tyr
195

<210> 223
<211> 70
<212> PRT
<213> Homo sapiens

<400> 223
Met Leu Leu His Leu Thr Ala Ala Phe Leu Gln Arg Ala Gln Phe Ser
1 5 10 15

Thr Tyr Phe Pro Gly Tyr Phe Asp Gly Gln Tyr Trp Leu Trp Trp Val
20 25 30

Phe Leu Val Leu Gly Phe Leu Leu Phe Leu Arg Gly Phe Ile Asn Tyr
35 40 45

Ala Lys Val Arg Lys Met Pro Glu Thr Phe Ser Asn Leu Pro Arg Thr
50 55 60

Arg Val Leu Phe Ile Tyr
65 70

<210> 224
<211> 82
<212> PRT
<213> Homo sapiens

<400> 224
Met Leu Thr Phe Phe Met Ala Phe Leu Phe Asn Trp Ile Gly Phe Phe
1 5 10 15

Leu Ser Phe Cys Leu Thr Thr Ser Ala Ala Gly Arg Tyr Gly Ala Ile
20 25 30

Ser Gly Phe Gly Leu Ser Leu Ile Lys Trp Ile Leu Ile Val Arg Phe
35 40 45

Ser Thr Tyr Phe Pro Ala Phe Met Asn Ser Leu Ser Arg Ser Lys Arg
50 55 60

Thr Pro Ala Gly Ser Glu Ser Arg Cys Arg Thr Gln Arg Asn Asn His
65 70 75 80

Leu Leu

<210> 225
<211> 45
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 225
Met Lys Lys Ser Leu Glu Asn Leu Asn Arg Leu Gln Val Met Leu Leu
1 5 10 15

His Leu Thr Ala Ala Phe Leu Gln Arg Ala His Xaa Ile Leu Thr Thr
20 25 30

Arg Met Ser Leu Gly Phe Gln Ser Pro His Leu Thr Met
35 40 45

<210> 226
<211> 33
<212> PRT
<213> Homo sapiens

<400> 226
Met Thr Val Met Asp Pro Lys Gln Met Asn Val Ala Ala Ala Val Trp
1 5 10 15

Ala Val Val Ser Tyr Val Val Ala Asp Met Glu Glu Met Leu Pro Arg
20 25 30

Ser

<210> 227
<211> 189
<212> PRT
<213> Homo sapiens

<400> 227
Pro Arg Val Arg Ser Arg Glu Pro Val Ala Gly Ala Pro Gly Cys Gly
1 5 10 15

Thr Ala Gly Pro Pro Ala Met Ala Thr Leu Trp Gly Gly Leu Leu Arg
20 25 30

Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser Val Leu Leu
35 40 45

Leu Ala His Cys Gln Thr Pro Pro Ser Asp Cys Leu His Val Val Glu
50 55 60

Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu Arg Cys
65 70 75 80

Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val Thr Ile
85 90 95

Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met Val Tyr
100 105 110

Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly His Ala
115 120 125

Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro Phe Ala

```
    130                 135                 140

Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn Val Leu
145                 150                 155                 160

Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val Gln Glu
                165                 170                 175

Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser
            180                 185
```

<210> 228
<211> 231
<212> PRT
<213> Homo sapiens

<400> 228

```
Met Ala Thr Leu Trp Gly Gly Leu Leu Arg Leu Gly Ser Leu Leu Ser
  1               5                  10                  15

Leu Ser Cys Leu Ala Leu Ser Val Leu Leu Leu Ala His Cys Gln Thr
             20                  25                  30

Pro Pro Arg Ile Ser Arg Met Ser Asp Val Asn Val Ser Ala Leu Pro
         35                  40                  45

Ile Lys Lys Asn Ser Gly His Ile Tyr Asn Lys Asn Ile Ser Gln Lys
     50                  55                  60

Asp Cys Asp Cys Leu His Val Val Glu Pro Met Pro Val Arg Gly Pro
 65                  70                  75                  80

Asp Val Glu Ala Tyr Cys Leu Arg Cys Glu Cys Lys Tyr Glu Glu Arg
                 85                  90                  95

Ser Ser Val Thr Ile Lys Val Thr Ile Ile Ile Tyr Leu Ser Ile Leu
            100                 105                 110

Gly Leu Leu Leu Leu Tyr Met Val Tyr Leu Thr Leu Val Glu Pro Ile
        115                 120                 125

Leu Lys Arg Arg Leu Phe Gly His Ala Gln Leu Ile Gln Ser Asp Asp
    130                 135                 140

Asp Ile Gly Asp His Gln Pro Phe Ala Asn Ala His Asp Val Leu Ala
145                 150                 155                 160

Arg Ser Arg Ser Arg Ala Asn Val Leu Asn Lys Val Glu Tyr Gly Thr
                165                 170                 175

Ala Ala Leu Glu Ala Ser Ser Pro Arg Ala Ala Lys Ser Leu Ser Leu
            180                 185                 190

Thr Gly Met Leu Ser Ser Ala Asn Trp Gly Ile Glu Phe Lys Val Thr
        195                 200                 205

Arg Lys Lys Gln Ala Asp Asn Trp Lys Gly Thr Asp Trp Val Leu Leu
    210                 215                 220
```

```
Gly Phe Ile Leu Ile Pro Cys
225                 230


<210> 229
<211> 456
<212> PRT
<213> Homo sapiens

<400> 229
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
 65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                 85                  90                  95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145                 150                 155                 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165                 170                 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180                 185                 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195                 200                 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210                 215                 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
                245                 250                 255
```

```
Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
385                 390                 395                 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
                405                 410                 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
            420                 425                 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
        435                 440                 445

Cys Ser Asn Asp Cys Pro Arg Arg
    450                 455


<210> 230
<211> 558
<212> PRT
<213> Homo sapiens

<400> 230
Met Ala Ala Ala Gly Arg Leu Pro Ser Ser Trp Ala Leu Phe Ser Pro
  1               5                  10                  15

Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
             20                  25                  30

Ala Leu His Asn Val Thr Ala Glu Leu Phe Gly Ala Glu Ala Trp Gly
         35                  40                  45

Thr Leu Ala Ala Phe Gly Asp Leu Asn Ser Asp Lys Gln Thr Asp Leu
     50                  55                  60

Phe Val Leu Arg Glu Arg Asn Asp Leu Ile Val Phe Leu Ala Asp Gln
```

```
65                  70                  75                  80

Asn Ala Pro Tyr Phe Lys Pro Lys Val Lys Val Ser Phe Lys Asn His
                85                  90                  95

Ser Ala Leu Ile Thr Ser Val Val Pro Gly Asp Tyr Asp Gly Asp Ser
            100                 105                 110

Gln Met Asp Val Leu Leu Thr Tyr Leu Pro Lys Asn Tyr Ala Lys Ser
        115                 120                 125

Glu Leu Gly Ala Val Ile Phe Trp Gly Gln Asn Gln Thr Leu Asp Pro
    130                 135                 140

Asn Asn Met Thr Ile Leu Asn Arg Thr Phe Gln Asp Glu Pro Leu Ile
145                 150                 155                 160

Met Asp Phe Asn Gly Asp Leu Ile Pro Asp Ile Phe Gly Ile Thr Asn
                165                 170                 175

Glu Ser Asn Gln Pro Gln Ile Leu Leu Gly Gly Asn Leu Ser Trp His
            180                 185                 190

Pro Ala Leu Thr Thr Thr Ser Lys Met Arg Ile Pro His Ser His Ala
        195                 200                 205

Phe Ile Asp Leu Thr Glu Asp Phe Thr Ala Asp Leu Phe Leu Thr Thr
    210                 215                 220

Leu Asn Ala Thr Thr Ser Thr Phe Gln Phe Glu Ile Trp Glu Asn Leu
225                 230                 235                 240

Asp Gly Asn Phe Ser Val Ser Thr Ile Leu Glu Lys Pro Gln Asn Met
                245                 250                 255

Met Val Val Gly Gln Ser Ala Phe Ala Asp Phe Asp Gly Asp Gly His
            260                 265                 270

Met Asp His Leu Leu Pro Gly Cys Glu Asp Lys Asn Cys Gln Lys Ser
        275                 280                 285

Thr Ile Tyr Leu Val Arg Ser Gly Met Lys Gln Trp Val Pro Val Leu
    290                 295                 300

Gln Asp Phe Ser Asn Lys Gly Thr Leu Trp Gly Phe Val Pro Phe Val
305                 310                 315                 320

Asp Glu Gln Gln Pro Thr Glu Ile Pro Ile Pro Ile Thr Leu His Ile
                325                 330                 335

Gly Asp Tyr Asn Met Asp Gly Tyr Pro Asp Ala Leu Val Ile Leu Lys
            340                 345                 350

Asn Thr Ser Gly Ser Asn Gln Gln Ala Phe Leu Leu Glu Asn Val Pro
        355                 360                 365

Cys Asn Asn Ala Ser Cys Glu Glu Ala Arg Arg Met Phe Lys Val Tyr
    370                 375                 380

Trp Glu Leu Thr Asp Leu Asn Gln Ile Lys Asp Ala Met Val Ala Thr
```

150

385 390 395 400

Phe Phe Asp Ile Tyr Glu Asp Gly Ile Leu Asp Ile Val Val Leu Ser
405 410 415

Lys Gly Tyr Thr Lys Asn Asp Phe Ala Ile His Thr Leu Lys Asn Asn
420 425 430

Phe Glu Ala Asp Ala Tyr Phe Val Lys Val Ile Val Leu Ser Gly Leu
435 440 445

Cys Ser Asn Asp Cys Pro Arg Lys Ile Thr Pro Phe Gly Val Asn Gln
450 455 460

Pro Gly Pro Tyr Ile Met Tyr Thr Thr Val Asp Ala Asn Gly Tyr Leu
465 470 475 480

Lys Asn Gly Ser Ala Gly Gln Leu Ser Gln Ser Ala His Leu Ala Leu
485 490 495

Gln Leu Pro Tyr Asn Val Leu Gly Leu Gly Arg Ser Ala Asn Phe Leu
500 505 510

Asp His Leu Tyr Val Gly Ile Pro Arg Pro Ser Gly Glu Lys Ser Ile
515 520 525

Arg Lys Gln Glu Trp Thr Ala Ile Ile Pro Asn Ser Gln Leu Ile Val
530 535 540

Ile Pro Tyr Pro His Asn Val Pro Arg Ser Trp Ser Ala Lys
545 550 555

<210> 231
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (144)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (168)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 231
Met Thr Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu
1 5 10 15

Asp Phe Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala
20 25 30

Asn Thr Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu
35 40 45

Ile Trp Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln

151

50 55 60

Met Asn Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala
65 70 75 80

Ser Cys Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly
85 90 95

Lys Lys Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly
100 105 110

His Ser Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg
115 120 125

Met Ala Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa
130 135 140

Val Glu Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg
145 150 155 160

Phe Glu Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro
165 170 175

Asn Ala Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr
180 185 190

Asn Thr Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly
195 200 205

Glu Cys Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala
210 215 220

Ser Cys Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His
225 230 235 240

Arg Ala Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn
245 250 255

Glu Ser Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu
260 265 270

Thr Leu Lys Ser Leu Gly Ala Leu Lys Lys
275 280

<210> 232
<211> 456
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (318)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (342)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 232
Val Ile Arg His Glu Gly Ser Thr Asn Met Glu Leu Ser Gln Met Ser
1 5 10 15

Xaa Leu Met Gly Leu Ser Val Leu Leu Gly Leu Leu Ala Leu Met Ala
20 25 30

Thr Ala Ala Val Xaa Arg Gly Trp Leu Arg Ala Gly Glu Glu Arg Ser
35 40 45

Gly Arg Pro Ala Cys Gln Lys Ala Asn Gly Phe Pro Pro Asp Lys Ser
50 55 60

Ser Gly Ser Lys Lys Gln Lys Gln Tyr Gln Arg Ile Arg Lys Glu Lys
65 70 75 80

Pro Gln Gln His Asn Phe Thr His Arg Leu Leu Ala Ala Ala Leu Lys
85 90 95

Ser His Ser Gly Asn Ile Ser Cys Met Asp Phe Ser Ser Asn Gly Lys
100 105 110

Tyr Leu Ala Thr Cys Ala Asp Asp Arg Thr Ile Arg Ile Trp Ser Thr
115 120 125

Lys Asp Phe Leu Gln Arg Glu His Arg Ser Met Arg Ala Asn Val Glu
130 135 140

Leu Asp His Ala Thr Leu Val Arg Phe Ser Pro Asp Cys Arg Ala Phe
145 150 155 160

Ile Val Trp Leu Ala Asn Gly Asp Thr Leu Arg Val Phe Lys Met Thr
165 170 175

Lys Arg Glu Asp Gly Gly Tyr Thr Phe Thr Ala Thr Pro Glu Asp Phe
180 185 190

Pro Lys Lys His Lys Ala Pro Val Ile Asp Ile Gly Ile Ala Asn Thr
195 200 205

Gly Lys Phe Ile Met Thr Ala Ser Ser Asp Thr Thr Val Leu Ile Trp
210 215 220

Ser Leu Lys Gly Gln Val Leu Ser Thr Ile Asn Thr Asn Gln Met Asn
225 230 235 240

Asn Thr His Ala Ala Val Ser Pro Cys Gly Arg Phe Val Ala Ser Cys
245 250 255

```
Gly Phe Thr Pro Asp Val Lys Val Trp Glu Val Cys Phe Gly Lys Lys
            260                 265                 270

Gly Glu Phe Gln Glu Val Val Arg Ala Phe Glu Leu Lys Gly His Ser
        275                 280                 285

Ala Ala Val His Ser Phe Ala Phe Ser Asn Asp Ser Arg Arg Met Ala
    290                 295                 300

Ser Val Ser Lys Asp Gly Thr Trp Lys Leu Trp Asp Thr Xaa Val Glu
305                 310                 315                 320

Tyr Lys Lys Lys Gln Asp Pro Tyr Leu Leu Lys Thr Gly Arg Phe Glu
                325                 330                 335

Glu Ala Ala Gly Ala Xaa Pro Cys Arg Leu Ala Leu Ser Pro Asn Ala
            340                 345                 350

Gln Val Leu Ala Leu Ala Ser Gly Ser Ser Ile His Leu Tyr Asn Thr
        355                 360                 365

Arg Arg Gly Glu Lys Glu Glu Cys Phe Glu Arg Val His Gly Glu Cys
    370                 375                 380

Ile Ala Asn Leu Ser Phe Asp Ile Thr Gly Arg Phe Leu Ala Ser Cys
385                 390                 395                 400

Gly Asp Arg Ala Val Arg Leu Phe His Asn Thr Pro Gly His Arg Ala
                405                 410                 415

Met Val Glu Glu Met Gln Gly His Leu Lys Arg Ala Ser Asn Glu Ser
            420                 425                 430

Thr Arg Gln Arg Leu Gln Gln Gln Leu Thr Gln Ala Gln Glu Thr Leu
        435                 440                 445

Lys Ser Leu Gly Ala Leu Lys Lys
    450                 455
```

<210> 233
<211> 363
<212> PRT
<213> Homo sapiens

<400> 233

```
Met Ser Val Met Val Val Arg Lys Lys Val Thr Arg Lys Trp Glu Lys
  1               5                  10                  15

Leu Pro Gly Arg Asn Thr Phe Cys Cys Asp Gly Arg Val Met Met Ala
             20                  25                  30

Arg Gln Lys Gly Ile Phe Tyr Leu Thr Leu Phe Leu Ile Leu Gly Thr
         35                  40                  45

Cys Thr Leu Phe Phe Ala Phe Glu Cys Arg Tyr Leu Ala Val Gln Leu
     50                  55                  60

Ser Pro Ala Ile Pro Val Phe Ala Ala Met Leu Phe Leu Phe Ser Met
```

154

```
65                  70                  75                  80

Ala Thr Leu Leu Arg Thr Ser Phe Ser Asp Pro Gly Val Ile Pro Arg
                 85                  90                  95

Ala Leu Pro Asp Glu Ala Ala Phe Ile Glu Met Glu Ile Glu Ala Thr
            100                 105                 110

Asn Gly Ala Val Pro Gln Gly Gln Arg Pro Pro Pro Arg Ile Lys Asn
        115                 120                 125

Phe Gln Ile Asn Asn Gln Ile Val Lys Leu Lys Tyr Cys Tyr Thr Cys
    130                 135                 140

Lys Ile Phe Arg Pro Pro Arg Ala Ser His Cys Ser Ile Cys Asp Asn
145                 150                 155                 160

Cys Val Glu Arg Phe Asp His His Cys Pro Trp Val Gly Asn Cys Val
                165                 170                 175

Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr Leu Phe Ile Leu Ser Leu Ser
            180                 185                 190

Leu Leu Thr Ile Tyr Val Phe Ala Phe Asn Ile Val Tyr Val Ala Leu
        195                 200                 205

Lys Ser Leu Lys Ile Gly Phe Leu Glu Thr Leu Lys Glu Thr Pro Gly
    210                 215                 220

Thr Val Leu Glu Val Leu Ile Cys Phe Phe Thr Leu Trp Ser Val Val
225                 230                 235                 240

Gly Leu Thr Gly Phe His Thr Phe Leu Val Ala Leu Asn Gln Thr Thr
                245                 250                 255

Asn Glu Asp Ile Lys Gly Ser Trp Thr Gly Lys Asn Arg Val Gln Asn
            260                 265                 270

Pro Tyr Ser His Gly Asn Ile Val Lys Asn Cys Cys Glu Val Leu Cys
        275                 280                 285

Gly Pro Leu Pro Pro Ser Val Leu Asp Arg Arg Gly Ile Leu Pro Leu
    290                 295                 300

Glu Glu Ser Gly Ser Arg Pro Pro Ser Thr Gln Glu Thr Ser Ser Ser
305                 310                 315                 320

Leu Leu Pro Gln Ser Pro Ala Pro Thr Glu Leu Asn Ser Asn Glu Met
                325                 330                 335

Pro Glu Asp Ser Ser Thr Pro Glu Glu Met Pro Pro Pro Glu Pro Pro
            340                 345                 350

Glu Pro Pro Gln Glu Ala Ala Glu Ala Glu Lys
        355                 360
```

<210> 234
<211> 184

<212> PRT
<213> Homo sapiens

<400> 234
Met Leu Phe Leu Phe Ser Met Ala Thr Leu Leu Arg Thr Ser Phe Ser
1 5 10 15

Asp Pro Gly Val Ile Pro Arg Ala Leu Pro Asp Glu Ala Ala Phe Ile
20 25 30

Glu Met Glu Ile Glu Ala Thr Asn Gly Ala Val Pro Gln Gly Gln Arg
35 40 45

Pro Pro Pro Arg Ile Lys Asn Phe Gln Ile Asn Asn Gln Ile Val Lys
50 55 60

Leu Lys Tyr Cys Tyr Thr Cys Lys Ile Phe Arg Pro Pro Arg Ala Ser
65 70 75 80

His Cys Ser Ile Cys Asp Asn Cys Val Glu Arg Phe Asp His His Cys
85 90 95

Pro Trp Val Gly Asn Cys Val Gly Lys Arg Asn Tyr Arg Tyr Phe Tyr
100 105 110

Leu Phe Ile Leu Ser Leu Ser Leu Leu Thr Ile Tyr Val Phe Ala Phe
115 120 125

Asn Ile Val Tyr Val Ala Leu Lys Ser Leu Lys Ile Gly Phe Leu Glu
130 135 140

Thr Leu Lys Gly Asn Ser Trp Asn Cys Ser Arg Ser Pro His Leu Leu
145 150 155 160

Leu Tyr Thr Leu Val Arg Arg Gly Thr Asp Trp Ile Ser Tyr Phe Pro
165 170 175

Arg Gly Ser Gln Pro Asp Asn Gln
180

<210> 235
<211> 52
<212> PRT
<213> Homo sapiens

<400> 235
Leu His Glu Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr
1 5 10 15

Pro Trp Leu Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser
20 25 30

Pro Pro Trp Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro
35 40 45

Pro Cys Gly Leu
50

<210> 236
<211> 177
<212> PRT
<213> Homo sapiens

<400> 236
Met Leu Pro Leu Leu Ile Ile Cys Leu Leu Pro Ala Ile Glu Gly Lys
1 5 10 15

Asn Cys Leu Arg Cys Trp Pro Glu Leu Ser Ala Leu Ile Asp Tyr Asp
20 25 30

Leu Gln Ile Leu Trp Val Thr Pro Gly Pro Pro Thr Glu Leu Ser Gln
35 40 45

Ser Ile His Ser Leu Phe Leu Glu Asp Asn Asn Phe Leu Lys Pro Trp
50 55 60

Tyr Leu Asp Arg Asp His Leu Glu Glu Glu Thr Ala Lys Phe Phe Thr
65 70 75 80

Gln Val His Gln Ala Ile Lys Thr Leu Arg Asp Asp Lys Thr Val Leu
85 90 95

Leu Glu Glu Ile Tyr Thr His Lys Asn Leu Phe Thr Glu Arg Leu Asn
100 105 110

Lys Ile Ser Asp Gly Leu Lys Glu Lys Gly Ala Pro Pro Leu His Glu
115 120 125

Cys Leu Pro Gly Ser Ile Ser Tyr Leu His Pro Arg Thr Pro Trp Leu
130 135 140

Cys Leu Pro Pro Gln His Leu Ser Phe Ser Thr Phe Ser Pro Pro Trp
145 150 155 160

Gln Pro Ala Met Ser Pro Val Pro Gly Thr Gly Gly Pro Pro Cys Gly
165 170 175

Leu

<210> 237
<211> 95
<212> PRT
<213> Homo sapiens

<400> 237
Pro Pro Val Pro Pro Trp Ile Ser Leu Pro Leu Thr Gly Ser Pro Pro
1 5 10 15

Arg Pro Gly Phe Val Pro Val Ser Pro Phe Cys Phe Ser Pro Met Thr
20 25 30

Asn Gly His Gln Val Leu Leu Leu Leu Leu Leu Thr Ser Ala Val Ala
35 40 45

```
Ala Gly Pro Trp Pro Gln Val His Ala Gly Gln Trp Gly Trp Met Cys
     50                  55                  60

Leu Pro Pro Gly Leu Pro Ser Val Gln Ala Arg Ser Gly Leu Gly Gly
 65                  70                  75                  80

Leu Pro Gly Gly Pro Gln Trp Val Pro Gly Gly Ala Arg Gly Tyr
                 85                  90                  95
```

<210> 238
<211> 404
<212> PRT
<213> Homo sapiens

<400> 238

```
Ile Gln Gln Trp Gly Asp Ser Val Leu Gly Arg Arg Cys Arg Asp Leu
  1               5                  10                  15

Leu Leu Gln Leu Tyr Leu Gln Arg Pro Glu Leu Arg Val Pro Val Pro
            20                  25                  30

Glu Val Leu Leu His Ser Glu Gly Ala Ala Ser Ser Ser Val Cys Lys
        35                  40                  45

Leu Asp Gly Leu Ile His Arg Phe Ile Thr Leu Leu Ala Asp Thr Ser
     50                  55                  60

Asp Ser Arg Ala Leu Glu Asn Arg Gly Ala Asp Ala Ser Met Ala Cys
 65                  70                  75                  80

Arg Lys Leu Ala Val Ala His Pro Leu Leu Leu Leu Arg His Leu Pro
                 85                  90                  95

Met Ile Ala Ala Leu Leu His Gly Arg Thr His Leu Asn Phe Gln Glu
            100                 105                 110

Phe Arg Gln Gln Asn His Leu Ser Cys Phe Leu His Val Leu Gly Leu
        115                 120                 125

Leu Glu Leu Leu Gln Pro His Val Phe Arg Ser Glu His Gln Gly Ala
    130                 135                 140

Leu Trp Asp Cys Leu Leu Ser Phe Ile Arg Leu Leu Leu Asn Tyr Arg
145                 150                 155                 160

Lys Ser Ser Arg His Leu Ala Ala Phe Ile Asn Lys Phe Val Gln Phe
                165                 170                 175

Ile His Lys Tyr Ile Thr Tyr Asn Ala Pro Ala Ala Ile Ser Phe Leu
            180                 185                 190

Gln Lys His Ala Asp Pro Leu His Asp Leu Ser Phe Asp Asn Ser Asp
        195                 200                 205

Leu Val Met Leu Lys Ser Leu Leu Ala Gly Leu Ser Leu Pro Ser Arg
    210                 215                 220
```

```
Asp Asp Arg Thr Asp Arg Gly Leu Asp Glu Glu Gly Glu Glu Glu Ser
225                 230                 235                 240

Ser Ala Gly Ser Leu Pro Leu Val Ser Val Ser Leu Phe Thr Pro Leu
                245                 250                 255

Thr Ala Ala Glu Met Ala Pro Tyr Met Lys Arg Leu Ser Arg Gly Gln
            260                 265                 270

Thr Val Glu Asp Leu Leu Glu Val Leu Ser Asp Ile Asp Glu Met Ser
        275                 280                 285

Arg Arg Arg Pro Glu Ile Leu Ser Phe Phe Ser Thr Asn Leu Gln Arg
    290                 295                 300

Leu Met Ser Ser Ala Glu Glu Cys Cys Arg Asn Leu Ala Phe Ser Leu
305                 310                 315                 320

Ala Leu Arg Ser Met Gln Asn Ser Pro Ser Ile Ala Ala Ala Phe Leu
                325                 330                 335

Pro Thr Phe Met Tyr Cys Leu Gly Ser Gln Asp Phe Glu Val Val Gln
            340                 345                 350

Thr Ala Leu Arg Asn Leu Pro Glu Tyr Ala Leu Leu Cys Gln Glu His
        355                 360                 365

Ala Ala Val Leu Leu His Arg Ala Phe Leu Val Gly Met Tyr Gly Gln
    370                 375                 380

Met Asp Pro Ser Ala Gln Ile Ser Glu Ala Leu Arg Ile Leu His Met
385                 390                 395                 400

Glu Ala Val Met
```

<210> 239
<211> 361
<212> PRT
<213> Homo sapiens

<400> 239

```
Met Leu Leu Lys His Leu Gln Arg Met Val Ser Val Pro Gln Val Lys
  1               5                  10                  15

Ala Ser Ala Leu Lys Val Val Thr Leu Thr Ala Asn Asp Lys Thr Ser
             20                  25                  30

Val Ser Phe Ser Ser Leu Pro Gly Gln Gly Val Ile Tyr Asn Val Ile
         35                  40                  45

Val Trp Asp Pro Phe Leu Asn Thr Ser Ala Ala Tyr Ile Pro Ala His
     50                  55                  60

Thr Tyr Ala Cys Ser Phe Glu Ala Gly Glu Gly Ser Cys Ala Ser Leu
 65                  70                  75                  80

Gly Arg Val Ser Ser Lys Val Phe Phe Thr Leu Phe Ala Leu Leu Gly
```

```
                85                  90                  95

Phe Phe Ile Cys Phe Phe Gly His Arg Phe Trp Lys Thr Glu Leu Phe
            100                 105                 110

Phe Ile Gly Phe Ile Ile Met Gly Phe Phe Phe Tyr Ile Leu Ile Thr
        115                 120                 125

Arg Leu Thr Pro Ile Lys Tyr Asp Val Asn Leu Ile Leu Thr Ala Val
    130                 135                 140

Thr Gly Ser Val Gly Gly Met Phe Leu Val Ala Val Trp Trp Arg Phe
145                 150                 155                 160

Gly Ile Leu Ser Ile Cys Met Leu Cys Val Gly Leu Val Leu Gly Phe
                165                 170                 175

Leu Ile Ser Ser Val Thr Phe Phe Thr Pro Leu Gly Asn Leu Lys Ile
            180                 185                 190

Phe His Asp Asp Gly Val Phe Trp Val Thr Phe Ser Cys Ile Ala Ile
        195                 200                 205

Leu Ile Pro Val Val Phe Met Gly Cys Leu Arg Ile Leu Asn Ile Leu
    210                 215                 220

Thr Cys Gly Val Ile Gly Ser Tyr Ser Val Val Leu Ala Ile Asp Ser
225                 230                 235                 240

Tyr Trp Ser Thr Ser Leu Ser Tyr Ile Thr Leu Asn Val Leu Lys Arg
                245                 250                 255

Ala Leu Asn Lys Asp Phe His Arg Ala Phe Thr Asn Val Pro Phe Gln
            260                 265                 270

Thr Asn Asp Phe Ile Ile Leu Ala Val Trp Gly Met Leu Ala Val Ser
        275                 280                 285

Gly Ile Thr Leu Gln Ile Arg Arg Glu Arg Gly Arg Pro Phe Phe Pro
    290                 295                 300

Pro His Pro Tyr Lys Leu Trp Lys Gln Glu Arg Glu Arg Arg Val Thr
305                 310                 315                 320

Asn Ile Leu Asp Pro Ser Tyr His Ile Pro Pro Leu Arg Glu Arg Leu
                325                 330                 335

Tyr Gly Arg Leu Thr Gln Ile Lys Gly Leu Phe Gln Lys Glu Gln Pro
            340                 345                 350

Ala Gly Glu Arg Thr Pro Leu Leu Leu
        355                 360
```

<210> 240
<211> 116
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (40)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 240
Trp Ala Arg Leu Arg Gly Pro Gly Ala His Ala Arg Thr Ser Pro Gln
1 5 10 15

Pro Trp Arg Gly Pro Ser Pro Ala Gln Ala Ala Met Gly Phe Leu Gln
20 25 30

Leu Leu Val Val Xaa Val Leu Xaa Ser Glu His Arg Val Ala Gly Ala
35 40 45

Ala Glu Val Phe Gly Asn Ser Ser Glu Gly Leu Ile Glu Phe Ser Val
50 55 60

Gly Lys Phe Arg Tyr Phe Glu Leu Asn Arg Pro Phe Pro Glu Glu Ala
65 70 75 80

Ile Leu His Asp Ile Ser Ser Asn Val Thr Phe Leu Ile Phe Gln Ile
85 90 95

His Ser Gln Tyr Gln Asn Thr Thr Val Ser Phe Ser Pro Arg Arg Arg
100 105 110

Ser Pro Thr Met
115

<210> 241
<211> 166
<212> PRT
<213> Homo sapiens

<400> 241
Pro Arg Val Arg Pro Ala Ser Pro Pro Val Arg Ser Pro Ala Arg Trp
1 5 10 15

Gly Ser Met Ala Gly Ser Pro Leu Leu Trp Gly Pro Arg Ala Gly Gly
20 25 30

Val Gly Leu Leu Val Leu Leu Leu Leu Gly Leu Phe Arg Pro Pro Pro
35 40 45

Ala Leu Cys Ala Arg Pro Val Lys Glu Pro Arg Gly Leu Ser Ala Ala
50 55 60

Ser Pro Pro Leu Ala Arg Leu Ala Leu Leu Ala Ala Ser Gly Gly Gln
65 70 75 80

Cys Pro Glu Val Arg Arg Arg Gly Arg Cys Arg Pro Gly Ala Gly Ala
85 90 95

```
Gly Ala Ser Ala Gly Ala Glu Arg Gln Glu Arg Ala Arg Ala Glu Ala
            100                 105                 110

Gln Arg Leu Arg Ile Ser Arg Arg Ala Ser Trp Arg Ser Cys Cys Ala
        115                 120                 125

Ser Gly Ala Pro Pro Ala Thr Leu Ile Arg Leu Trp Ala Trp Thr Thr
    130                 135                 140

Thr Pro Thr Arg Leu Gln Arg Ser Ser Leu Ala Leu Cys Ser Ala Pro
145                 150                 155                 160

Ala Leu Thr Leu Pro Pro
                165
```

<210> 242
<211> 414
<212> PRT
<213> Homo sapiens

<400> 242

```
Pro Arg Val Arg Leu Ala Thr Pro Asn Ile Trp Asp Leu Ser Met Leu
  1               5                  10                  15

Phe Ala Phe Ile Ser Leu Leu Val Met Leu Pro Thr Trp Trp Ile Val
             20                  25                  30

Ser Ser Trp Leu Val Trp Gly Val Ile Leu Phe Val Tyr Leu Val Ile
         35                  40                  45

Arg Ala Leu Arg Leu Trp Arg Thr Ala Lys Leu Gln Val Thr Leu Lys
     50                  55                  60

Lys Tyr Ser Val His Leu Glu Asp Met Ala Thr Asn Ser Arg Ala Phe
 65                  70                  75                  80

Thr Asn Leu Val Arg Lys Ala Leu Arg Leu Ile Gln Glu Thr Glu Val
                 85                  90                  95

Ile Ser Arg Gly Phe Thr Leu Val Ser Ala Ala Cys Pro Phe Asn Lys
            100                 105                 110

Ala Gly Gln His Pro Ser Gln His Leu Ile Gly Leu Arg Lys Ala Val
        115                 120                 125

Tyr Arg Thr Leu Arg Ala Asn Phe Gln Ala Ala Arg Leu Ala Thr Leu
    130                 135                 140

Tyr Met Leu Lys Asn Tyr Pro Leu Asn Ser Glu Ser Asp Asn Val Thr
145                 150                 155                 160

Asn Tyr Ile Cys Val Val Pro Phe Lys Glu Leu Gly Leu Gly Leu Ser
                165                 170                 175

Glu Glu Gln Ile Ser Glu Glu Glu Ala His Asn Phe Thr Asp Gly Phe
            180                 185                 190
```

```
Ser Leu Pro Ala Leu Lys Val Leu Phe Gln Leu Trp Val Ala Gln Ser
        195                 200                 205

Ser Glu Phe Phe Arg Arg Leu Ala Leu Leu Leu Ser Thr Ala Asn Ser
    210                 215                 220

Pro Pro Gly Pro Leu Leu Thr Pro Ala Leu Leu Pro His Arg Ile Leu
225                 230                 235                 240

Ser Asp Val Thr Gln Gly Leu Pro His Ala His Ser Ala Cys Leu Glu
                245                 250                 255

Glu Leu Lys Arg Ser Tyr Glu Phe Tyr Arg Tyr Phe Glu Thr Gln His
            260                 265                 270

Gln Ser Val Pro Gln Cys Leu Ser Lys Thr Gln Gln Lys Ser Arg Glu
        275                 280                 285

Leu Asn Asn Val His Thr Ala Val Arg Ser Leu Gln Leu His Leu Lys
    290                 295                 300

Ala Leu Leu Asn Glu Val Ile Ile Leu Glu Asp Glu Leu Glu Lys Leu
305                 310                 315                 320

Val Cys Thr Lys Glu Thr Gln Glu Leu Val Ser Glu Ala Tyr Pro Ile
                325                 330                 335

Leu Glu Gln Lys Leu Lys Leu Ile Gln Pro His Val Gln Ala Ser Asn
            340                 345                 350

Asn Cys Trp Glu Glu Ala Ile Ser Gln Val Asp Lys Leu Leu Arg Arg
        355                 360                 365

Asn Thr Asp Lys Lys Gly Lys Pro Glu Ile Ala Cys Glu Asn Pro His
    370                 375                 380

Cys Thr Val Ser Thr Phe Glu Ala Ala Tyr Ser Thr His Cys Arg Gln
385                 390                 395                 400

Arg Ser Asn Pro Arg Gly Ala Gly Ile Arg Ser Leu Cys Arg
                405                 410
```

<210> 243
<211> 145
<212> PRT
<213> Homo sapiens

<400> 243

```
Ala Ala Pro His Pro Pro Leu Leu Arg Pro Leu Cys Leu Trp Cys Pro
  1               5                  10                  15

Leu Trp Pro Ala Trp Pro Leu Arg Gly Arg Pro Arg Ser Ala Trp Lys
             20                  25                  30

Arg Trp Pro Pro Leu Pro Val Gly Pro Ala Lys Leu Gly Cys Ser Met
         35                  40                  45

Thr Thr Arg Gln Pro Thr Ala Val Ser Trp Pro Cys Trp Leu Met Ser
```

```
     50                  55                  60

Ser Ser Leu Ser Thr Ala Cys Leu Ala Trp Thr Leu Thr Gly Ser Leu
 65                  70                  75                  80

Ala Arg Glu Ala Thr Arg Arg Ala Arg Ser Leu Ser Pro Thr Trp Asn
                85                  90                  95

Cys Ser Ala Arg Gln Val Pro Pro Ser Pro Pro His Ser Gly Leu Gly
            100                 105                 110

Arg Arg Gly Trp Ala His Cys His Leu Thr Cys Leu Leu Val Thr Gln
        115                 120                 125

Leu Phe Arg Val Gly Arg Ile His Pro Ile Leu Ser Leu Pro Leu Val
    130                 135                 140

Thr
145
```

<210> 244
<211> 72
<212> PRT
<213> Homo sapiens

<400> 244

```
Leu Gln Leu Ala Ser Gln Ser Ala Gly Ile Lys Gly Met Ser His Cys
  1               5                  10                  15

Ala Arg Pro Thr Phe Leu Thr Leu Leu Leu Ala Ser Cys Phe Trp Ala
             20                  25                  30

Ala Ala Ile Pro Asn Arg Asn Val Ile Leu Ser Val Ser Phe Arg Pro
         35                  40                  45

Leu His Met Gln Phe Thr Leu Ser Ile Leu Val Phe Ile Leu Arg Ile
     50                  55                  60

Leu Ile Leu Leu Arg Ser Phe Leu
 65                  70
```

<210> 245
<211> 140
<212> PRT
<213> Homo sapiens

<400> 245

```
Met Val Leu Val Leu Arg His Pro Leu Cys Ala Arg Glu Arg Ala Phe
  1               5                  10                  15

Arg Glu Pro Gly Arg Gly Leu Leu Thr Arg Thr Gly Gln His Asp Gly
             20                  25                  30

Ala Pro Ala Val Thr Ala Val Pro Gly Pro Leu Gly Ala Val Ala Ala
         35                  40                  45
```

```
Ala Glu Gly Arg Arg Ser Ala Trp Gly Ala Gly Gly Ser Ser Pro Pro
     50                  55                  60

Arg Lys Val Leu Trp Gly Asp Met Arg Gly Arg Arg Ala Gly Val Asp
 65                  70                  75                  80

Val Leu Gly Pro Ala Leu Ser Ser Glu Ala Ala Gly Ala Glu Ala Arg
                85                  90                  95

Gly Trp Gly Met Pro Gly Met Gly Val Gly Val Gly Ala Ser Glu Thr
            100                 105                 110

Arg Gly Ala Leu Phe Leu Gly Arg Glu Gly Val His Gly Pro Cys Pro
        115                 120                 125

Met Asp Gly Leu Gly Pro Trp Pro Trp Gly Pro Trp
    130                 135                 140
```

<210> 246
<211> 353
<212> PRT
<213> Homo sapiens

<400> 246

```
Met Gly Pro Ala Val Lys Met Trp Thr Asn Ala Trp Lys Gly Leu Asp
  1               5                  10                  15

Asp Cys His Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg
            20                  25                  30

Cys Ser Cys Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys
        35                  40                  45

Leu Asp Val Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln
     50                  55                  60

Cys His Asn Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln
 65                  70                  75                  80

Thr Leu Leu Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly
                85                  90                  95

Gln Asn Val Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu
            100                 105                 110

Arg Pro Trp Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser
        115                 120                 125

Leu Arg Pro Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys
    130                 135                 140

Pro Pro Gly Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu
145                 150                 155                 160

Cys Arg Val Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly
                165                 170                 175
```

165

Ser Tyr Gln Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly
180 185 190

Lys Asn Cys Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys
195 200 205

Gly Pro Gly Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val
210 215 220

Asp Thr Pro Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr
225 230 235 240

Cys Phe Arg Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr
245 250 255

Leu Gln Tyr Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His
260 265 270

Asp Val Ala Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn
275 280 285

Arg Thr Glu Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala
290 295 300

Leu Arg Pro Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala
305 310 315 320

Leu Thr Arg Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro
325 330 335

Arg His Gln Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro
340 345 350

Tyr

<210> 247
<211> 146
<212> PRT
<213> Homo sapiens

<400> 247
Met Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala
1 5 10 15

Arg Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys
20 25 30

Phe Arg Gln Ser His Thr Trp Ser Leu Leu Gln Gly Ala Ala His Asp
35 40 45

Asp Pro Val Ala Arg Gly Leu Asp Pro Asp Gly Leu Leu Leu Leu Asp
50 55 60

Val Val Val Asn Gly Val Val Pro Gly Arg Ala Trp Leu Thr Gln Ile
65 70 75 80

Phe Lys Cys Arg Thr Leu Lys Lys His Tyr Val Gln Thr Arg Ala Trp

```
                85                  90                  95

Pro Ala Val Arg Gly Leu His Thr Ala Leu Leu Pro Gly Arg Pro Pro
            100                 105                 110

Leu Val Pro Thr Leu Gln Pro Gln His Pro Val Gln Arg Gly Pro Gly
        115                 120                 125

Pro Pro Ala Pro Ala Gly Ala Ala Pro Ala Gly Leu Ser Tyr Gln Leu
    130                 135                 140

Gly Leu
145
```

<210> 248
<211> 638
<212> PRT
<213> Homo sapiens

<400> 248

```
His Ala Ser Gly Ala Phe Leu Val Val Arg Gly Glu Pro Gln Gly Ser
  1               5                  10                  15

Trp Gly Ser Met Thr Gly Val Ile Asn Gly Arg Lys Phe Gly Val Ala
             20                  25                  30

Thr Leu Asn Thr Ser Val Met Gln Glu Ala His Ser Gly Val Ser Ser
         35                  40                  45

Ile His Ser Ser Ile Arg His Val Pro Ala Asn Val Gly Pro Leu Met
     50                  55                  60

Arg Val Leu Val Val Thr Ile Ala Pro Ile Tyr Trp Ala Leu Ala Arg
 65                  70                  75                  80

Glu Ser Gly Glu Ala Leu Asn Gly His Ser Leu Thr Gly Gly Lys Phe
                 85                  90                  95

Arg Gln Glu Ser His Val Glu Phe Ala Thr Gly Glu Leu Leu Thr Met
            100                 105                 110

Thr Gln Trp Pro Gly Val Trp Ile Pro Met Ala Ser Cys Ser Ser Thr
        115                 120                 125

Trp Trp Ser Met Ala Leu Ser Pro Asp Ser Leu Ala Asp Ala Asp Leu
    130                 135                 140

Gln Val Gln Asp Phe Glu Glu His Tyr Val Gln Thr Gly Pro Gly Gln
145                 150                 155                 160

Leu Phe Val Gly Ser Thr Gln Arg Phe Phe Gln Gly Gly Leu Pro Ser
                165                 170                 175

Phe Leu Arg Cys Asn His Ser Ile Gln Tyr Asn Ala Ala Arg Gly Pro
            180                 185                 190

Gln Pro Gln Leu Val Gln His Leu Arg Ala Ser Ala Ile Ser Ser Ala
        195                 200                 205
```

```
Phe Asp Pro Glu Ala Glu Ala Leu Arg Phe Gln Leu Ala Thr Ala Leu
    210                 215                 220

Gln Ala Glu Glu Asn Glu Val Gly Cys Pro Glu Gly Phe Glu Leu Asp
225                 230                 235                 240

Ser Gln Gly Ala Phe Cys Val Asp Val Asp Glu Cys Ala Trp Asp Ala
                245                 250                 255

His Leu Cys Arg Glu Gly Gln Arg Cys Val Asn Leu Leu Gly Ser Tyr
            260                 265                 270

Arg Cys Leu Pro Asp Cys Gly Pro Gly Phe Arg Val Ala Asp Gly Ala
        275                 280                 285

Gly Cys Glu Asp Val Asp Glu Cys Leu Glu Gly Leu Asp Asp Cys His
    290                 295                 300

Tyr Asn Gln Leu Cys Glu Asn Thr Pro Gly Gly His Arg Cys Ser Cys
305                 310                 315                 320

Pro Arg Gly Tyr Arg Met Gln Gly Pro Ser Leu Pro Cys Leu Asp Val
                325                 330                 335

Asn Glu Cys Leu Gln Leu Pro Lys Ala Cys Ala Tyr Gln Cys His Asn
            340                 345                 350

Leu Gln Gly Ser Tyr Arg Cys Leu Cys Pro Pro Gly Gln Thr Leu Leu
        355                 360                 365

Arg Asp Gly Lys Ala Cys Thr Ser Leu Glu Arg Asn Gly Gln Asn Val
    370                 375                 380

Thr Thr Val Ser His Arg Gly Pro Leu Leu Pro Trp Leu Arg Pro Trp
385                 390                 395                 400

Ala Ser Ile Pro Gly Thr Ser Tyr His Ala Trp Val Ser Leu Arg Pro
                405                 410                 415

Gly Pro Met Ala Leu Ser Ser Val Gly Arg Ala Trp Cys Pro Pro Gly
            420                 425                 430

Phe Ile Arg Gln Asn Gly Val Cys Thr Asp Leu Asp Glu Cys Arg Val
        435                 440                 445

Arg Asn Leu Cys Gln His Ala Cys Arg Asn Thr Glu Gly Ser Tyr Gln
    450                 455                 460

Cys Leu Cys Pro Ala Gly Tyr Arg Leu Leu Pro Ser Gly Lys Asn Cys
465                 470                 475                 480

Gln Asp Ile Asn Glu Cys Glu Glu Glu Ser Ile Glu Cys Gly Pro Gly
                485                 490                 495

Gln Met Cys Phe Asn Thr Arg Gly Ser Tyr Gln Cys Val Asp Thr Pro
            500                 505                 510

Cys Pro Ala Thr Tyr Arg Gln Gly Pro Ser Pro Gly Thr Cys Phe Arg
        515                 520                 525
```

```
Arg Cys Ser Gln Asp Cys Gly Thr Gly Gly Pro Ser Thr Leu Gln Tyr
    530                 535                 540

Arg Leu Leu Pro Leu Pro Leu Gly Val Arg Ala His His Asp Val Ala
545                 550                 555                 560

Arg Leu Thr Ala Phe Ser Glu Val Gly Val Pro Ala Asn Arg Thr Glu
                565                 570                 575

Leu Ser Met Leu Glu Pro Asp Pro Arg Ser Pro Phe Ala Leu Arg Pro
            580                 585                 590

Leu Arg Ala Gly Leu Gly Ala Val Tyr Thr Arg Arg Ala Leu Thr Arg
        595                 600                 605

Ala Gly Leu Tyr Arg Leu Thr Val Arg Ala Ala Ala Pro Arg His Gln
    610                 615                 620

Ser Val Phe Val Leu Leu Ile Ala Val Ser Pro Tyr Pro Tyr
625                 630                 635
```

<210> 249
<211> 367
<212> PRT
<213> Homo sapiens

<400> 249

```
Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn His Pro Glu
  1               5                  10                  15

Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp Pro Gly Glu
             20                  25                  30

Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro Lys Glu Phe
         35                  40                  45

Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg Ser Glu Ile Gln
     50                  55                  60

Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser His His Met Gln
 65                  70                  75                  80

Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu Leu Lys Gln Trp
                 85                  90                  95

Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu Pro Thr Glu Ser
            100                 105                 110

Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr Pro Leu Phe Leu
        115                 120                 125

Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr Leu Ala Leu Trp
    130                 135                 140

Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln Ala Val Arg Asp
145                 150                 155                 160
```

```
Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln Glu Asn Thr Cys
                165                 170                 175

Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala Ser Ile Ala Leu
            180                 185                 190

Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln Gln Trp Asp Gln
        195                 200                 205

Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu Leu Gly Glu Ser
    210                 215                 220

Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln Val Glu Glu Asp
225                 230                 235                 240

Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala Glu Thr Leu Ile
                245                 250                 255

Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu Leu Ser Lys Ser
            260                 265                 270

Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His Leu Gln Arg Met
        275                 280                 285

Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe Arg Glu Leu Pro
    290                 295                 300

Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr Arg Leu Arg Ile
305                 310                 315                 320

Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu Ala Phe Leu Glu
                325                 330                 335

Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val Trp Asp Ser Tyr
            340                 345                 350

Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala Ala Cys
        355                 360                 365
```

<210> 250
<211> 124
<212> PRT
<213> Homo sapiens

<400> 250

```
Met Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val
  1               5                  10                  15

Leu Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu
             20                  25                  30

Ser Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro
         35                  40                  45

Val Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val
     50                  55                  60

Met Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu
```

```
                                                    170
 65                  70                  75                  80

Pro Ser Cys Thr Asp Gln Cys Phe Arg Ala Lys Pro His Ser Trp Gly
                 85                  90                  95

His Phe Ser Arg Phe Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys
            100                 105                 110

Thr Arg Asn Glu Phe Arg Leu Pro Ala Arg Ala Asp
        115                 120
```

<210> 251
<211> 674
<212> PRT
<213> Homo sapiens

<400> 251

```
Met Thr Gly Arg Glu Phe Phe Ser Arg Phe Pro Glu Leu Tyr Pro Phe
  1               5                  10                  15

Leu Leu Lys Gln Leu Glu Thr Val Ala Asn Thr Val Asp Ser Asp Met
            20                  25                  30

Gly Glu Pro Asn Arg His Pro Ser Met Phe Leu Leu Leu Leu Val Leu
        35                  40                  45

Glu Arg Leu Tyr Ala Ser Pro Met Asp Gly Thr Ser Ser Ala Leu Ser
    50                  55                  60

Met Gly Pro Phe Val Pro Phe Ile Met Arg Cys Gly His Ser Pro Val
65                  70                  75                  80

Tyr His Ser Arg Glu Met Ala Ala Arg Ala Leu Val Pro Phe Val Met
                85                  90                  95

Ile Asp His Ile Pro Asn Thr Ile Arg Thr Leu Leu Ser Thr Leu Pro
            100                 105                 110

Ser Cys Thr Asp Gln Cys Phe Arg Gln Asn His Ile His Gly Thr Leu
        115                 120                 125

Leu Gln Val Phe His Leu Leu Gln Ala Tyr Ser Asp Ser Lys His Gly
    130                 135                 140

Thr Asn Ser Asp Phe Gln His Glu Leu Thr Asp Ile Thr Val Cys Thr
145                 150                 155                 160

Lys Ala Lys Leu Trp Leu Ala Lys Arg Gln Asn Pro Cys Leu Val Thr
                165                 170                 175

Arg Ala Val Tyr Ile Asp Ile Leu Phe Leu Leu Thr Cys Cys Leu Asn
            180                 185                 190

Arg Ser Ala Lys Asp Asn Gln Pro Val Leu Glu Ser Leu Gly Phe Trp
        195                 200                 205

Glu Glu Val Arg Gly Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly Phe
    210                 215                 220
```

```
Pro Trp Ala Phe Lys Val Pro Gly Leu Pro Gln Tyr Leu Gln Ser Leu
225                 230                 235                 240

Thr Arg Leu Ala Ile Ala Ala Val Trp Ala Ala Ala Ala Lys Ser Gly
                245                 250                 255

Glu Arg Glu Thr Asn Val Pro Ile Ser Phe Ser Gln Leu Leu Glu Ser
            260                 265                 270

Ala Phe Pro Glu Val Arg Ser Leu Thr Leu Glu Ala Leu Leu Glu Lys
        275                 280                 285

Phe Leu Ala Ala Ala Ser Gly Leu Gly Glu Lys Gly Val Pro Pro Leu
    290                 295                 300

Leu Cys Asn Met Gly Glu Lys Phe Leu Leu Leu Ala Met Lys Glu Asn
305                 310                 315                 320

His Pro Glu Cys Phe Cys Lys Ile Leu Lys Ile Leu His Cys Met Asp
                325                 330                 335

Pro Gly Glu Trp Leu Pro Gln Thr Glu His Cys Val His Leu Thr Pro
            340                 345                 350

Lys Glu Phe Leu Ile Trp Thr Met Asp Ile Ala Ser Asn Glu Arg Ser
        355                 360                 365

Glu Ile Gln Ser Val Ala Leu Arg Leu Ala Ser Lys Val Ile Ser His
    370                 375                 380

His Met Gln Thr Cys Val Glu Asn Arg Glu Leu Ile Ala Ala Glu Leu
385                 390                 395                 400

Lys Gln Trp Val Gln Leu Val Ile Leu Ser Cys Glu Asp His Leu Pro
                405                 410                 415

Thr Glu Ser Arg Leu Ala Val Val Glu Val Leu Thr Ser Thr Thr Pro
            420                 425                 430

Leu Phe Leu Thr Asn Pro His Pro Ile Leu Glu Leu Gln Asp Thr Leu
        435                 440                 445

Ala Leu Trp Lys Cys Val Leu Thr Leu Leu Gln Ser Glu Glu Gln Ala
    450                 455                 460

Val Arg Asp Ala Ala Thr Glu Thr Val Thr Thr Ala Met Ser Gln Glu
465                 470                 475                 480

Asn Thr Cys Gln Ser Thr Glu Phe Ala Phe Cys Gln Val Asp Ala Ser
                485                 490                 495

Ile Ala Leu Ala Leu Ala Leu Ala Val Leu Cys Asp Leu Leu Gln Gln
            500                 505                 510

Trp Asp Gln Leu Ala Pro Gly Leu Pro Ile Leu Leu Gly Trp Leu Leu
        515                 520                 525

Gly Glu Ser Asp Asp Leu Val Ala Cys Val Glu Ser Met His Gln Val
    530                 535                 540
```

```
Glu Glu Asp Tyr Leu Phe Glu Lys Ala Glu Val Asn Phe Trp Ala Glu
545                 550                 555                 560

Thr Leu Ile Phe Val Lys Tyr Leu Cys Lys His Leu Phe Cys Leu Leu
                565                 570                 575

Ser Lys Ser Gly Trp Arg Pro Pro Ser Pro Glu Met Leu Cys His Leu
            580                 585                 590

Gln Arg Met Val Ser Glu Gln Cys His Leu Leu Ser Gln Phe Phe Arg
        595                 600                 605

Glu Leu Pro Pro Ala Ala Glu Phe Val Lys Thr Val Glu Phe Thr Arg
    610                 615                 620

Leu Arg Ile Gln Glu Glu Arg Thr Leu Ala Cys Leu Arg Leu Leu Ala
625                 630                 635                 640

Phe Leu Glu Gly Lys Glu Gly Glu Asp Thr Leu Val Leu Ser Val Trp
                645                 650                 655

Asp Ser Tyr Ala Glu Ser Arg Gln Leu Thr Leu Pro Arg Thr Glu Ala
            660                 665                 670

Ala Cys
```

<210> 252
<211> 10
<212> PRT
<213> Homo sapiens

<400> 252
Ile Ile Ser Gly Ser Glu Leu Ile Thr Gly
1   5   10

<210> 253
<211> 230
<212> PRT
<213> Homo sapiens

<400> 253

```
Val Asp Gly Ile Asp Lys Leu Asp Ile Glu Phe Leu Gln Gln Phe Leu
  1               5                  10                  15

Glu Thr His Ser Arg Gly Pro Arg Leu His Ser Pro Gly His Ala Ser
             20                  25                  30

Gln Glu Ala Thr Pro Gly Ala Asn Met Ser Ser Gly Thr Glu Leu Leu
         35                  40                  45

Trp Pro Gly Ala Ala Leu Leu Val Leu Leu Gly Val Ala Ala Ser Leu
     50                  55                  60

Cys Val Arg Cys Ser Arg Pro Gly Ala Lys Arg Ser Glu Lys Ile Tyr
```

65 70 75 80

Gln Gln Arg Ser Leu Arg Glu Asp Gln Gln Ser Phe Thr Gly Ser Arg
85 90 95

Thr Tyr Ser Leu Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met
100 105 110

Ala Pro Thr Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu Glu
115 120 125

Asp Pro Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg His
130 135 140

Gly Ser Glu Glu Ala Tyr Ile Asp Pro Ile Ala Met Glu Tyr Tyr Asn
145 150 155 160

Trp Gly Arg Phe Ser Lys Pro Pro Glu Asp Asp Asp Ala Asn Ser Tyr
165 170 175

Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly Ala Gln
180 185 190

Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp Leu Ser Leu Ser Leu
195 200 205

Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys Pro Ser Ala Ser Pro
210 215 220

Glu Glu Asp Glu Gly Ile
225 230

<210> 254
<211> 25
<212> PRT
<213> Homo sapiens

<400> 254
Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg His Gly Ser
1 5 10 15

Glu Glu Ala Tyr Ile Asp Pro Ile Ala
20 25

<210> 255
<211> 21
<212> PRT
<213> Homo sapiens

<400> 255
Met Glu Tyr Tyr Asn Trp Gly Arg Phe Ser Lys Pro Pro Glu Asp Asp
1 5 10 15

Asp Ala Asn Ser Tyr
20

<210> 256
<211> 27
<212> PRT
<213> Homo sapiens

<400> 256
Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly Ala Gln
1 5 10 15

Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp
20 25

<210> 257
<211> 27
<212> PRT
<213> Homo sapiens

<400> 257
Leu Ser Leu Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys
1 5 10 15

Pro Ser Ala Ser Pro Glu Glu Asp Glu Gly Ile
20 25

<210> 258
<211> 68
<212> PRT
<213> Homo sapiens

<400> 258
Val Arg Cys Ser Arg Pro Gly Ala Lys Arg Ser Glu Lys Ile Tyr Gln
1 5 10 15

Gln Arg Ser Leu Arg Glu Asp Gln Gln Ser Phe Thr Gly Ser Arg Thr
20 25 30

Tyr Ser Leu Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met Ala
35 40 45

Pro Thr Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu Glu Asp
50 55 60

Pro Ala Ser Ser
65

<210> 259
<211> 122
<212> PRT
<213> Homo sapiens

<400> 259
Val Leu Trp Arg Glu Ala Ser Ala Leu Val Leu Ser Asn Arg Leu Ser

175

```
  1               5                  10                  15

Ser Gly Leu Leu His Asp Leu Leu Leu Gln Pro Ala Ile His Ser Arg
            20                  25                  30

Leu Phe Pro Arg Arg Ser Arg Gly Leu Ser Glu Gly Glu Gly Ser Ser
        35                  40                  45

Val Ser Leu Gln Arg Ser Arg Val Leu Ser Ala Met Lys His Val Leu
    50                  55                  60

Asn Leu Tyr Leu Leu Gly Val Val Leu Thr Leu Leu Ser Ile Phe Val
65                  70                  75                  80

Arg Val Met Glu Ser Leu Glu Gly Leu Leu Glu Ser Pro Ser Pro Gly
                85                  90                  95

Thr Ser Trp Thr Thr Arg Ser Gln Leu Ala Asn Thr Glu Pro Thr Lys
            100                 105                 110

Gly Leu Pro Asp His Pro Ser Arg Ser Met
        115                 120
```

<210> 260
<211> 129
<212> PRT
<213> Homo sapiens

<400> 260

```
Tyr Thr Phe His Thr Gln Ile Phe Leu Asp Phe Pro Met Ile Phe Leu
  1               5                  10                  15

Thr Val Leu Pro Leu Ala Phe Leu Phe Leu His Ser Gly Phe Tyr His
            20                  25                  30

Tyr Ile Ser Phe Ser Cys Leu Phe Ser Leu Ser Leu Ala Leu Phe Phe
        35                  40                  45

Phe Leu Asp Val Ala Thr Phe Arg Arg Pro Gly Gln Leu Phe Cys Glu
    50                  55                  60

Arg Ser Val Leu Phe Asp Met Phe His Phe Gly Phe Val Ser Leu Phe
65                  70                  75                  80

Leu His Glu Trp Ile Gln Ala Lys His Phe Trp Ala Gly Leu Phe Ile
                85                  90                  95

Val Leu Pro Ser Asp Val Phe Phe Ser Val His His Leu Glu Ala Pro
            100                 105                 110

Asp Gly Ser Phe Pro Asn Ile Ala Lys Leu Ser Leu Ile Ile Leu Leu
        115                 120                 125

Arg
```

<210> 261
<211> 99
<212> PRT
<213> Homo sapiens

<400> 261
Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
1 5 10 15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
20 25 30

Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
35 40 45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
50 55 60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
65 70 75 80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
85 90 95

Phe Phe Pro

<210> 262
<211> 51
<212> PRT
<213> Homo sapiens

<400> 262
Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn Cys Ile Phe Phe
1 5 10 15

Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile Thr Ala Ile Ser
20 25 30

Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile Phe Phe Pro Cys
35 40 45

Leu Leu Ala
50

<210> 263
<211> 259
<212> PRT
<213> Homo sapiens

<400> 263
Gly Thr Arg Phe Pro Thr Gly Glu Thr Pro Ser Leu Gly Phe Thr Val
1 5 10 15

Thr Leu Val Leu Leu Asn Ser Leu Ala Phe Leu Leu Met Ala Val Ile
20 25 30

```
Tyr Thr Lys Leu Tyr Cys Asn Leu Glu Lys Glu Asp Leu Ser Glu Asn
         35                  40                  45

Ser Gln Ser Ser Met Ile Lys His Val Ala Trp Leu Ile Phe Thr Asn
     50                  55                  60

Cys Ile Phe Phe Cys Pro Val Ala Phe Phe Ser Phe Ala Pro Leu Ile
 65                  70                  75                  80

Thr Ala Ile Ser Ile Ser Pro Glu Ile Met Lys Ser Val Thr Leu Ile
                 85                  90                  95

Phe Phe Pro Leu Pro Ala Cys Leu Asn Pro Val Leu Tyr Val Phe Phe
            100                 105                 110

Asn Pro Lys Phe Lys Glu Asp Trp Lys Leu Leu Lys Arg Arg Val Thr
        115                 120                 125

Lys Lys Ser Gly Ser Val Ser Val Ser Ile Ser Ser Gln Gly Gly Cys
    130                 135                 140

Leu Glu Gln Asp Phe Tyr Tyr Asp Cys Gly Met Tyr Ser His Leu Gln
145                 150                 155                 160

Gly Asn Leu Thr Val Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys
                165                 170                 175

Pro Val Ser Cys Lys His Leu Ile Lys Ser His Ser Cys Pro Ala Leu
            180                 185                 190

Ala Val Ala Ser Cys Gln Arg Pro Glu Gly Tyr Trp Ser Asp Cys Gly
        195                 200                 205

Thr Gln Ser Ala His Ser Asp Tyr Ala Asp Glu Glu Asp Ser Phe Val
    210                 215                 220

Ser Asp Ser Ser Asp Gln Val Gln Ala Cys Gly Arg Ala Cys Phe Tyr
225                 230                 235                 240

Gln Ser Arg Gly Phe Pro Leu Val Arg Tyr Ala Tyr Asn Leu Pro Arg
                245                 250                 255

Val Lys Asp
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<210> 264
<211> 22
<212> PRT
<213> Homo sapiens

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<400> 264
Cys Asp Cys Cys Glu Ser Phe Leu Leu Thr Lys Pro Val Ser Cys Lys
  1               5                  10                  15

His Leu Ile Lys Ser His
            20
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<210> 265
<211> 81
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 265
Ala Leu Glu Asn Ser Gly Ser Pro Gly Leu Gln Asp Ser Ala Arg Ala
1 5 10 15

His Phe Asn Xaa Ser Leu Arg Ser Phe Ser Phe Leu Arg Asn Gln Met
20 25 30

Tyr Ile Phe Glu Leu Ser Leu Tyr Leu Glu Gly Thr Ser Phe Val Val
35 40 45

Val Leu Leu Phe Leu Leu Ile Ser Val Ser Leu Asp Ser Pro Pro Thr
50 55 60

Thr Lys Gly Trp Asp Ser Val Leu His Ile Trp Val Pro Leu Ile Val
65 70 75 80

Gln

<210> 266
<211> 77
<212> PRT
<213> Homo sapiens

<400> 266
Gly His Glu Ser Ile Cys Gly Ser Cys Arg Ser Trp Ile Tyr Phe Ser
1 5 10 15

Ile Arg Cys Arg Arg Arg Met Arg Pro Trp Trp Ser Leu Leu Leu Glu
20 25 30

Ala Cys Ala Thr Cys Ala Gln Thr Gly Pro Thr Arg Ser Thr Ser Cys
35 40 45

Thr Gln Glu Val Ser His Ser Ser Ser Thr Ala Tyr Pro Ala Pro Met
50 55 60

Arg Arg Arg Cys Cys Leu Pro Ser Pro Arg Ser Cys Thr
65 70 75

<210> 267
<211> 119
<212> PRT
<213> Homo sapiens

<400> 267
Lys Arg Ala Gly Val Glu Val Gly Gly Leu Val Met Ala Leu Ala Gly
1 5 10 15

Ser Val Phe Val Leu Gly Gly Val Leu Val Leu Cys Val Glu Arg Asn
20 25 30

Gly Glu Gly Glu Met Gly Trp Pro Gln His Leu Pro Lys Ser Gln Pro
35 40 45

Leu Ser Pro Pro Val Ala Val Arg Arg Cys Ser Phe Glu Arg Ser Trp
50 55 60

Ile Asp Leu Leu Val Glu Thr Ser Ser Ser Met Val Thr Cys Arg Gln
65 70 75 80

Gln Val Gly Thr Pro Asn Gly Met Glu Gly Arg Gly Gly Gly Pro Lys
85 90 95

Thr Thr Phe Pro Ile Arg Leu Gln Leu Ser Gly Ala Cys Ala Val Arg
100 105 110

Pro Glu Ile Gln Trp Glu Val
115

<210> 268
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (94)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (192)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 268
Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro Phe Glu Lys Cys Met
1 5 10 15

Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val Thr Ile Leu Glu Ala
20 25 30

Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr Arg Asp Gln Xaa Thr
35 40 45

Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met Pro Ser Ser His Arg
50 55 60

```
Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu Asn Leu Thr Lys Phe
 65                  70                  75                  80

Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val His Glu Xaa Lys Leu
                85                  90                  95

Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys Leu Gly Tyr Ala Leu
            100                 105                 110

Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp Ile Tyr Gln Met Ala
        115                 120                 125

Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu Gly Cys Arg Lys Ala
    130                 135                 140

Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu Tyr Leu Leu Gly Glu
145                 150                 155                 160

Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu Gly Asp Val Met Ser
                165                 170                 175

Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu Ala Leu Arg Ala Xaa
            180                 185                 190

Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg Ile Val Gly Gly Trp
        195                 200                 205

Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu Ser Gly Leu Val Leu
    210                 215                 220

Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly Pro His Asp Val His
225                 230                 235                 240

Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn Leu Lys Val Leu Lys
                245                 250                 255

Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro Ala Val Lys Arg Ile
            260                 265                 270

Thr Phe Ser
        275
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<210> 269
<211> 212
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (123)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 269

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Leu Pro Arg His Met Gln Glu Ala Leu Arg Arg Leu His Tyr Val Pro
  1               5                  10                  15

Ala Thr Lys Val Phe Leu Ser Phe Arg Arg Pro Phe Trp Arg Glu Glu
```

181

```
            20                  25                  30

His Ile Glu Gly Gly His Ser Asn Thr Asp Arg Pro Ser Arg Met Ile
         35                  40                  45

Phe Tyr Pro Pro Pro Arg Glu Gly Ala Leu Leu Leu Ala Ser Tyr Thr
     50                  55                  60

Trp Ser Asp Ala Ala Ala Ala Phe Ala Gly Leu Ser Arg Glu Glu Ala
 65                  70                  75                  80

Leu Arg Leu Ala Leu Asp Asp Val Ala Ala Leu His Gly Pro Val Val
                 85                  90                  95

Arg Gln Leu Trp Asp Gly Thr Gly Val Val Lys Arg Trp Ala Glu Asp
            100                 105                 110

Gln His Ser Gln Gly Gly Phe Val Val Gln Xaa Pro Ala Leu Trp Gln
        115                 120                 125

Thr Glu Lys Asp Asp Trp Thr Val Pro Tyr Gly Arg Ile Tyr Phe Ala
    130                 135                 140

Gly Glu His Thr Ala Tyr Pro His Gly Trp Val Glu Thr Ala Val Lys
145                 150                 155                 160

Ser Ala Leu Arg Ala Ala Ile Lys Ile Asn Ser Arg Lys Gly Pro Ala
                165                 170                 175

Ser Asp Thr Ala Ser Pro Glu Gly His Ala Ser Asp Met Glu Gly Gln
            180                 185                 190

Gly His Val His Gly Val Ala Ser Ser Pro Ser His Asp Leu Ala Lys
        195                 200                 205

Glu Glu Gly Ser
    210
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<210> 270
<211> 319
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (68)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (213)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 270
Met Ala Pro Leu Ala Leu His Leu Leu Val Leu Val Pro Ile Leu Leu
1 5 10 15

Ser Leu Val Ala Ser Gln Asp Trp Lys Ala Glu Arg Ser Gln Asp Pro
20 25 30

Phe Glu Lys Cys Met Gln Asp Pro Asp Tyr Glu Gln Leu Leu Lys Val
35 40 45

Thr Ile Leu Glu Ala Asp Asn Arg Ile Gly Gly Arg Ile Phe Thr Tyr
50 55 60

Arg Asp Gln Xaa Thr Gly Trp Ile Gly Glu Leu Gly Ala Met Arg Met
65 70 75 80

Pro Ser Ser His Arg Ile Leu His Lys Leu Cys Gln Gly Leu Gly Leu
85 90 95

Asn Leu Thr Lys Phe Thr Gln Tyr Asp Lys Asn Thr Trp Thr Glu Val
100 105 110

His Glu Xaa Lys Leu Arg Asn Tyr Val Val Glu Lys Val Pro Glu Lys
115 120 125

Leu Gly Tyr Ala Leu Arg Pro Gln Glu Lys Gly His Ser Pro Glu Asp
130 135 140

Ile Tyr Gln Met Ala Leu Asn Gln Ala Leu Lys Asp Leu Lys Ala Leu
145 150 155 160

Gly Cys Arg Lys Ala Met Lys Lys Phe Glu Arg His Thr Leu Leu Glu
165 170 175

Tyr Leu Leu Gly Glu Gly Asn Leu Ser Arg Pro Ala Val Gln Leu Leu
180 185 190

Gly Asp Val Met Ser Glu Asp Gly Phe Phe Tyr Leu Ser Phe Ala Glu
195 200 205

Ala Leu Arg Ala Xaa Ser Cys Leu Ser Asp Arg Leu Gln Tyr Ser Arg
210 215 220

Ile Val Gly Gly Trp Asp Leu Leu Pro Arg Ala Leu Leu Ser Ser Leu
225 230 235 240

Ser Gly Leu Val Leu Leu Asn Ala Pro Val Val Ala Met Thr Gln Gly
245 250 255

Pro His Asp Val His Val Gln Ile Glu Thr Ser Pro Pro Ala Arg Asn
260 265 270

Leu Lys Val Leu Lys Ala Asp Val Val Leu Leu Thr Ala Ser Gly Pro
275 280 285

Ala Val Lys Arg Ile Thr Phe Ser Pro Arg Cys Pro Ala Thr Cys Arg
290 295 300

Arg Arg Cys Gly Gly Cys Thr Thr Cys Arg Pro Pro Arg Cys Ser
305 310 315

<210> 271
<211> 1102
<212> DNA
<213> Homo sapiens

<400> 271
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tggaggagaa gaggcattct ggtttttgga atttttagcc attttgctct ggtttcttcc 180
catctttgtg gatttatcta cctttcatct tcaatgttag tgacctatgg atggggtctc 240
tgagtggatg tgctcttcct ttctgtttgt tagttttctt tctaacagtt agcccctctg 300
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tactgggaga ttcctcccag tcaggataca aggaggtcag ggacctactt gaggaggcag 540
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ctctgtccca gggagatggg ggttttattt ttaagtcccc aactggggct gctgcctttt 720
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gagctgccgt tggctccacc cagttcaaac ttcccaaggg gctttgttta tactgtaagg 840
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tgtcccaggt tgatctcaga ctgctgctgt gctggcagtg agaatttcaa gccagtggat 960
cttagtttgc tgtgctctgt gggggtggga cccattgaac cagactactc ggctccctgg 1020
cttcagcccc ctttccagga gagtgaaggg ttctgtctca ttggcattcc aggagtcact 1080
ggtgtatgga aaaaaaaaag aa 1102

<210> 272
<211> 1102
<212> DNA
<213> Homo sapiens

<400> 272
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ttcatccaac tcattctcag tccagttttg tttccttgct ggtgaggagt tgtgatcctt 120
tggaggagaa gaggcattct ggtttttgga atttttagcc attttgctct ggtttcttcc 180
catctttgtg gatttatcta cctttcatct tcaatgttag tgacctatgg atggggtctc 240
tgagtggatg tgctcttcct ttctgtttgt tagttttctt tctaacagtt agcccctctg 300
ctgtaggtct gctggagttt gctggaggtc cactccagac cctgtttgcc tgggtatcac 360
cagtggaggc tgcagaacag caaagattgc ttcctgttct ttcctctgga agcttcgtct 420
cagaggggca cctgccagat gccagccaga gctctcctgt atgaggtgtc tgttggccca 480
tactggcaga ttcctcccag tcaggataca aggaggtcag gtacctactt gaggaggcag 540
tctgaccctt agcagaggtt gaacactgtg ctaggaggtc ctctgctctt ttcagagctg 600
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ctctgtccca gggagatggg ggttttattt ttaagtcccc aactggggct gctgcctttt 720
tttcagagat gccctgccca gagaggagaa atctggcagt ctggcctcag aggccttgct 780
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tgtcccaggt tgatctcaga ctgctgctgt gctggcagtg agaatttcaa gccagtggat 960
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cttcagcccc ctttccagga gagtgaaggg ttctgtctca ttggcattcc aggagtcact 1080
ggtgtatgga aaaaaaaaag aa 1102

<210> 273
<211> 185
<212> DNA
<213> Homo sapiens

<400> 273
tctgtatttc ctgaatttga atgttggcct gccttgctag gttggggaag ttctcctgga 60
taatatcctg aagaatgttt tccaacttgg ttacattctg cccatcaatt tcaggtacac 120
caaccaaatg tagatttggt cttttcacat agtcccatat ttcttggagg ctttgctcat 180
tcctt 185

<210> 274
<211> 185
<212> DNA
<213> Homo sapiens

<400> 274
tctgtatttc ctgaatttga atgttggcct gccttgctag gttggggaag ttctcctgga 60
taatatcctg aagaatgttt tccaacttgg ttacattctg cccatcaatt tcaggtacac 120
caaccaaatg tagatttggt cttttcacat agtcccatat ttcttggagg ctttgctcat 180
tcctt 185

<210> 275
<211> 950
<212> DNA
<213> Homo sapiens

<400> 275
ggcagctgca gagctccagg tttctctgcc cacaagggca ggggctgccc ctcgcccagg 60
atgactctgc cttccagagc cttggcctcc ctgggggtgg gagtgtgggg gatgctaagg 120
ttaaatcagg tcacagtaag ttgtgggggc agcaggtgga gcagcagagt ggcactggga 180
gctttctctt gggtgtgcgg tgtggccttg gttctgcagc catcaggtgg gggcttggga 240
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ccgggggggtt ccccctccta gaacatgcaa gctctcacac cggtgcgtca tcatcacacc 360
catcatcaag cccacagtgg tatactgaac acctgcccca caaagacggt ggaatgctct 420
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gacttacagc aaatgtttgt ttgctgaatg aattaattaa agataaagca 950

<210> 276
<211> 950
<212> DNA
<213> Homo sapiens

<400> 276
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ttaaatcagg tcacagtaag ttgtgggggc agcaggtgga gcagcagagt ggcactggga 180
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ggaaccacgc ctgctccagc ttcatacctc ccactgctac agcacagaac ctgcttctca 900
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<210> 277
<211> 297
<212> DNA
<213> Homo sapiens

<400> 277
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cctcccgagt agctgggact acaggcgccc accaccatgc ccagctaatt ttttttgtat 180
ttttagtaga gacagggttt caccgtgtta cccaggatgg tctccatctc ctgacctcgt 240
gatccacccg cctcggcctc ccaaagtgct gggattacag gcgtgagcca ctgcgcc 297

<210> 278
<211> 297
<212> DNA
<213> Homo sapiens

<400> 278
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cctcccgagt agctgggact acaggcgccc accaccatgc ccagctaatt ttttttgtat 180
ttttagtaga gacagggttt caccgtgtta cccaggatgg tctccatctc ctgacctcgt 240
gatccacccg cctcggcctc ccaaagtgct gggattacag gcgtgagcca ctgcgcc 297

<210> 279
<211> 4002
<212> DNA
<213> Homo sapiens

<400> 279
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cagtgacctg tcccagtgac cacacgtcct ggtggcggat gaagccctct tcgagctaga 180
gaaaaataga taagcccagc agccccagaa gatggtctga acagaggcat ctccgcaccc 240
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cggcgtccaa ggagactagg atgagttctt ggcaagggcc agcgttagaa atcactgtgg 360
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ggccgagttc aggccactgc tagctttctc atactcccac aggctagacc agagatgcca 2160
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<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<213> Homo sapiens

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<211> 1685
<212> DNA
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<212> DNA
<213> Homo sapiens

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<211> 335
<212> DNA
<213> Homo sapiens

<400> 340
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<210> 341
<211> 319
<212> DNA
<213> Homo sapiens

<400> 341
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cctatctcta caaaaagtt 319

<210> 342
<211> 468

<212> DNA
<213> Homo sapiens

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<210> 343
<211> 468
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<213> Homo sapiens

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<210> 344
<211> 319
<212> DNA
<213> Homo sapiens

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cctatctcta caaaaagtt 319

<210> 345
<211> 335
<212> DNA
<213> Homo sapiens

<400> 345
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<210> 346
<211> 730
<212> DNA
<213> Homo sapiens

<400> 346

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<210> 347
<211> 1676
<212> DNA
<213> Homo sapiens

<400> 347
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<211> 1676
<212> DNA
<213> Homo sapiens

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<210> 349
<211> 1675
<212> DNA
<213> Homo sapiens

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<210> 350

<211> 9268
<212> DNA
<213> Homo sapiens

<400> 350
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gcgctagggc gctggcaagt gtagcggtca cgctgcgcgt aaccaccaca cccgccgcgc 420

ttaatgcgcc gctacagggc gcgtccattc gccattcagg ctgcgcaact gttgggaagg 480
gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaaggggat gtgctgcaag 540
gcgattaagt tgggtaacgc cagggtttc ccagtcacga cgttgtaaaa cgacggccag 600
tgaattgtaa tacgactcac tatagggc 628

<210> 359
<211> 640
<212> DNA
<213> Homo sapiens

<400> 359
aaattgtaag cgttaatatt ttgttaaaat tcgcgttaaa tttttgttaa atcagctcat 60
tttttaacca ataggccgaa atcggcaaaa tcccttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaaggaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgctacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 360
<211> 513
<212> DNA
<213> Homo sapiens

<400> 360
gagtgttgtt ccagtttgga acaagagtcc actattaaag aacgtggact ccaacgtcaa 60
agggcgaaaa accgtctatc agggcgatgg cccactacgt gaaccatcac cctaatcaag 120
ttttttgggg tcgaggtgcc gtaaagcact aaatcggaac cctaaaggga gcccccgatt 180
tagagcttga cggggaaagc cggcgaacgt ggcgagaaag gaagggaaga aagcgaaagg 240
agcgggcgct agggcgctgg caagtgtagc ggtcacgctg cgcgtaacca ccacacccgc 300
cgcgcttaat gcgccgctac agggcgcgtc cattcgccat tcaggctgcg caactgttgg 360
gaagggcgat cggtgcgggc ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct 420
gcaaggcgat taagttgggt aacgccaggg ttttcccagt cacgacgttg taaaacgacg 480
gccagtgaat tgtaatacga ctcactatag ggc 513

<210> 361
<211> 612
<212> DNA
<213> Homo sapiens

<400> 361
ttcgcgttaa atttttgtta caatcagctc attgtttaac caataggccg aaatcggcaa 60
aatcccttat aaatcaaaag aatagaccga gatagggttg agtgttgttc cagtttggaa 120
caagagtcca ctattaaaga acgtggactc caacgtcaaa gggcgaaaaa ccgtctatca 180
gggcgatggc ccactacgtg aaccatcacc ctaatcaagt tttttggggt cgaggtgccg 240
taaagcacta aatcggaacc ctaaagggag cccccgattt agagcttgac ggggaaagcc 300
ggcgaacgtg gcgagaaagg aagggaagaa agcgaaagga gcgggcgcta gggcgctggc 360
aagtgtagcg gtcacgctgc gcgtaaccac cacacccgcc gcgcttaatg cgccgctaca 420
gggcgcgtcc attcgccatt caggctgcgc aactgttggg aagggcgatc ggtgcgggcc 480
tcttcgctat tacgccagct ggcgaaaggg ggatgtgctg caaggcgatt aagttgggta 540
acgccagggt tttcccagtc acgacgttgt aaaacgacgg ccagtgaatt gtaatacgac 600
tcactatagg gc 612

<210> 362
<211> 686
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (95)..(95)
<223> n equals a,t,g, or c

<400> 362
caccaaggcc agtttggaag cgaacggcta ccccgaaatt aagatactac agcgtgagtt 60
atgagaaagc gccacgcttc ccgagggaag aaagncggga cagttatccg gtagccggca 120
gggtcgaacc agaagagcgc acgaggagct tccaagggga aaacgcctgg tatctttata 180
gtcctgtcgg gtttcgccac ctctgacttg agcgtcgatt tttgtgatgc tcgtcagggg 240
ggcggagcct atggaaaaac gccagcaacg cggccttttt acggttcttg gccttttgct 300
ggccttttgc tcacatgttc tttcctgcgt tatcccctga ttctgtggat aaccgtatta 360
ccgcctttga gtgagctgat accgctcgcc gcagccgaac gaccgagcgc agcgagtcag 420
tgagcgagga agcggaagag cgcccaatac gcaaaccgcc tctccccgcg cgttggccga 480
ttcattaatg cagctggcac gacaggtttc ccgactggaa agcgggcagt gagcgcaacg 540
caattaatgt gagttagctc actcattagg caccccaggc tttacacttt atgcttccgg 600
ctcgtatgtt gtgtggaatt gtgagcggat aacaatttca cacaggaaac agctatgacc 660
atgattacga attcgagctc ggtacc 686

<210> 363
<211> 462
<212> DNA
<213> Homo sapiens

<400> 363
caacgtcaaa gggcgaaaaa ccgtctatca gggcgatggc ccactacgtg aaccatcacc 60
ctaatcaagt tttttggggt cgaggtgccg taaagcacta aatcggaacc ctaaagggag 120
cccccgattt agagcttgac ggggaaagcc ggcgaacgtg gcgagaaagg aagggaagaa 180
agcgaaagga gcgggcgcta gggcgctggc aagtgtagcg gtcacgctgc gcgtaaccac 240
cacacccgcc gcgcttaatg cgccgctaca gggcgcgtcc attcgccatt caggctgcgc 300
aactgttggg aagggcgatc ggtgcgggcc tcttcgmtat tacgccagct ggcgaaaggg 360
ggatgtgctg caaggcgatt aagttgggta acgccagggt tttcccagtc acgacgttgt 420
aaaacgacgg ccagtgaatt gtaatacgac tcactatagg gc 462

<210> 364
<211> 640
<212> DNA
<213> Homo sapiens

<400> 364
aaattgtaag cgttaatatt ttgttaaaat tcgcgttaaa tttttgttaa atcagctcat 60
ttttttaacca ataggccgaa atcggcaaaa tcccttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaaggaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgctacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 365
<211> 640
<212> DNA
<213> Homo sapiens

<400> 365

aaattgtaag cgttaatatt ttgttaaaat tcgcgttaaa tttttgttaa atcagctcat 60
tttttaacca ataggccgaa atcggcaaaa tcccttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaaggaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgctacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 366
<211> 654
<212> DNA
<213> Homo sapiens

<400> 366
aataccgcat caggaaattg taagcgttaa tattttgtta aaattcgcgt taaatttttg 60
ttaaatcagc tcatttttta accaataggc cgaaatcggc aaaatccctt ataaatcaaa 120
agaatagacc gagatagggt tgagtgttgt tccagtttgg aacaagagtc cactattaaa 180
gaacgtggac tccaacgtca aagggcgaaa aaccgtctat cagggcgatg gcccactacg 240
tgaaccatca ccctaatcaa gttttttggg gtcgaggtgc cgtaaagcac taaatcggaa 300
ccctaaaggg agcccccgat ttagagcttg acggggaaag ccggcgaacg tggcgagaaa 360
ggaagggaag aaagcgaaag gagcgggcgc tagggcgctg gcaagtgtag cggtcacgct 420
gcgcgtaacc accacacccg ccgcgcttaa tgcgccgcta cagggcgcgt ccattcgcca 480
ttcaggctgc gcaactgttg ggaagggcga tcggtgcggg cctcttcgct attacgccag 540
ctggcgaaag ggggatgtgc tgcaaggcga ttaagttggg taacgccagg gttttcccag 600
tcacgacgtt gtaaaacgac ggccagtgaa ttgtaatacg actcactata gggc 654

<210> 367
<211> 414
<212> DNA
<213> Homo sapiens

<400> 367
tgaaccatca ccctaatcaa gttttttggg gtggaggtgc cgtaaagcac taaatcggaa 60
ccctaaaggg agcccccgat ttagagcttg acggggaaag ccggcgaacg tggcgagaaa 120
ggaagggaag aaagcgaaag gagcgggcgc tagggcgctg gcaagtgtag cggtcacgct 180
gcgggtaacc accaccaccg ccgcgcttaa tgcgccgcta cagggcgcgt ccattcgcca 240
ttcaggctgc gcaactgttg ggaagggcga tcggtgcggg cctyttcgct attacgccag 300
ctggcgaaag ggggatgtgc tgcaaggcga ttaagttggg taacgccagg gttttcccag 360
tcacgacgtt gtaaaacgac ggccagtgaa ttgtaatacg actcactata gggc 414

<210> 368
<211> 647
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (29)..(29)
<223> n equals a,t,g, or c

<400> 368
cgcatcagga aatgtaagcg ttaatattnt gtaaaattcg cgttaaattt ttgttaaatc 60
agctcatttt ttaaccaata ggccgaaatc ggcaaaatcc cttataaatc aaaagaatag 120
accgagatag ggttgagtgt tgttccagtt tggaacaaga gtccactatt aaagaacgtg 180
gactccaacg tcaaagggcg aaaaaccgtc tatcagggcg atggcccact acgtgaacca 240
tcaccctaat caagtttttt ggggtcgagg tgccgtaaag cactaaatcg gaaccctaaa 300

gggagccccc gatttagagc ttgacgggga aagccggcga acgtggcgag aaaggaaggg 360
aagaaagcga aaggagcggg cgctagggcg ctggcaagtg tagcggtcac gctgcgcgta 420
accaccacac ccgccgcgct taatgcgccg ctacagggcg cgtccattcg ccattcaggc 480
tgcgcaactg ttgggaaggg cgatcggtgc gggcctcttc gctattacgc cagctggcga 540
aaggggatg tgctgcaagg cgattaagtt gggtaacgcc agggttttcc cagtcacgac 600
gttgtaaaac gacggccagt gaattgtaat acgactcact atagggc 647

<210> 369
<211> 640
<212> DNA
<213> Homo sapiens

<400> 369
aaattgtaag cgttaatatt ttgttaaaat tcgcgttaaa tttttgttaa atcagctcat 60
tttttaacca ataggccgaa atcggcaaaa tccsttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaagsaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgytacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 370
<211> 640
<212> DNA
<213> Homo sapiens

<400> 370
aaattgtaag cgttaatatt ttgttaagat tcgcgttaaa tttttgttaa atcagctcat 60
tttttaacca ataggccgaa atcggcaaaa tcccttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaaggaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgctacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 371
<211> 571
<212> DNA
<213> Homo sapiens

<400> 371
aataggccga aatcggcaaa atcccttata aatcaaaaga atagaccgag atagggttga 60
gtgttgttcc agtttggaac aagagtccac tattaaagaa cgtggactcc aacgtcaaag 120
ggcgaaaaac cgtctatcag ggcgatggcc cactacgtga accatcaccc taatcaagtt 180
ttttggggtc gaggtgccgt aaagcactaa atcggaaccc taaagggagc ccccgattta 240
gagcttgacg gggaaagccg gcgaacgtgg cgagaaagga agggaagaaa gcgaaaggag 300
cgggcgctag ggcgctggca agtgtagcgg tcacgctgcg cgtaaccacc acacccgccg 360
cgcttaatgc gccgctacag ggcgcgtcca ttcgccattc aggctgcgca actgttggga 420
agggcgatcg gtgcgggcct cttcgctatt acgccagctg gcgaaagggg gatgtgctgc 480
aaggcgatta agttgggtaa cgccagggtt ttcccagtca cgacgttgta aaacgacggc 540
cagtgaattg taatacgact cactataggg c 571

<210> 372
<211> 640
<212> DNA
<213> Homo sapiens

<400> 372
aaattgtaag cgttaatatt ttgttaaaat tcgcgttaaa tttttgttaa atcagctcat 60
tttttaacca ataggccgaa atcggcaaaa tcccttataa atcaaaagaa tagaccgaga 120
tagggttgag tgttgttcca gtttggaaca agagtccact attaaagaac gtggactcca 180
acgtcaaagg gcgaaaaacc gtctatcagg gcgatggccc actacgtgaa ccatcaccct 240
aatcaagttt tttggggtcg aggtgccgta aagcactaaa tcggaaccct aaagggagcc 300
cccgatttag agcttgacgg ggaaagccgg cgaacgtggc gagaaaggaa gggaagaaag 360
cgaaaggagc gggcgctagg gcgctggcaa gtgtagcggt cacgctgcgc gtaaccacca 420
cacccgccgc gcttaatgcg ccgctacagg gcgcgtccat tcgccattca ggctgcgcaa 480
ctgttgggaa gggcgatcgg tgcgggcctc ttcgctatta cgccagctgg cgaaaggggg 540
atgtgctgca aggcgattaa gttgggtaac gccagggttt tcccagtcac gacgttgtaa 600
aacgacggcc agtgaattgt aatacgactc actatagggc 640

<210> 373
<211> 639
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (88)..(88)
<223> n equals a,t,g, or c

<400> 373
aattgtaagc gttaatattt tgttaaaatt cgcgttaaat ttttgttaaa tcagctcatt 60
ttttaaccaa taggccgaaa tcggcaanat cccttataaa tcaaaagaat agaccgagat 120
agggttgagt gttgttccag tttggaacaa gagtccacta ttaaagaacg tggactccaa 180
cgtcaaaggg cgaaaaaccg tctatcaggg cgatggccca ctacgtgaac catcacccta 240
atcaagtttt ttggggtcga ggtgccgtaa agcactaaat cggaacccta aagggagccc 300
ccgatttaga gcttgacggg gaaagccggc gaacgtggcg agaaaggaag ggaagaaagc 360
gaaaggagcg ggcgctaggg cgctggcaag tgtagcggtc acgctgcgcg taaccaccac 420
acccgccgcg cttaatgcgc cgctacaggg cgcgtccatt cgccattcag gctgcgcaac 480
tgttgggaag ggcgatcggt gcgggcctct tcgctattac gccagctggc gaaaggggga 540
tgtgctgcaa ggcgattaag ttgggtaacg ccagggtttt cccagtcacg acgttgtaaa 600
acgacggcca gtgaattgta atacgactca ctatagggc 639

<210> 374
<211> 397
<212> DNA
<213> Homo sapiens

<400> 374
atcaagtttt ttggggtcga ggtgccgtga agcattaaat cggaacccta aagggagccc 60
ccgatttaga gcttgacggg gaaagccggc gaacgtggcg agaaaggaag ggaagaaagc 120
gaaaggagcg gacgttaggg cgctggcaag tgtagcggtc cgtgcgcgta accaccacac 180
acgctgcgct taatgcgccg ctacagggcg cgtccattcg ccattcgagg tgcgcaactg 240
ttgggaaggg cgatcggtgc gggcctcttc gctattacgc cagctggcga aaggggatg 300
tgctgcaagg cgattaagtt gggtaacgcc agggttttcc cagtcacgac gttgtaaaac 360
gacggccagt gaattgtaat acgactcact atagggc 397

<210> 375
<211> 648
<212> DNA
<213> Homo sapiens

<400> 375
gcatcaggma attgtaagcg ttaatatttt gttaaaattc gcgttaaatt tttgttaaat 60
cagctcattt tttaaccaat aggccgaaat cggcaaaatc ccttataaat caaaagaata 120
gaccgagata gggttgagtg ttgttccagt ttggaacaag agtccactat taaagaacgt 180
ggactccaac gtcaaagggc gaaaaaccgt ctatcagggc gatggcccac tacgtgaacc 240
atcaccctaa tcaagttttt tggggtcgag gtgccgtaaa gcactaaatc ggaaccctaa 300
agggagcccc cgatttagag cttgacgggg aaagccggcg aacgtggcga gaaaggaagg 360
gaagaaagcg aaaggagcgg gcgctagggc gctggcaagt gtagcggtca cgctgcgcgt 420
aaccaccaca cccgccgcgc ttaatgcgcc gctacagggc gcgtccattc gccattcagg 480
ctgcgcaact gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg 540
aaaggggat gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcacga 600
cgttgtaaaa cgacggccag tgaattgtaa tacgactcac tatagggc 648

<210> 376
<211> 434
<212> DNA
<213> Homo sapiens

<400> 376
gggcgatggc cccactaccg tgaaccatca ccctaatcaa gtttttttggg gtcgaggtgc 60
cgtaaagcac taaatcggaa ccctaaaggg agcccccgat ttagagcttg acggggaaag 120
ccggcgaacg tggcgagaaa ggaagggaag aaagcgaaag gagcgggcgc tagggcgctg 180
gcaagtgtag cggtcacgct gcgcgtaacc accacacccg ccgcgcttaa tgcgccgcta 240
cagggcgcgt ccattcgcca ttcaggctgc gcaactgttg ggaagggcga tcggtgcggg 300
cctcttcgct attacgccag ctggcgaaag ggggatgtgc tgcaaggcga ttaagttggg 360
taacgccagg gttttcccag tcacgacgtt gtaaaacgac ggccagtgaa ttgtaatacg 420
actcactata gggc 434

<210> 377
<211> 624
<212> DNA
<213> Homo sapiens

<400> 377
tattttgtta aaattcgcgt taaatttttg ttaaaccagc tcatttttta accaataggc 60
ggaaatcggc aaaatccctt ataaatcaaa agaatagacc gagatagggt tkagtgttgt 120
tccagtttgg aacaagagtc cactattaaa gaacgtggac tccaacgtca aagggcgaaa 180
aaccgtctat cagggcgatg gcccactacg tgaaccatca ccctaatcaa gtttttttggg 240
gtcgaggtgc cgtaaagcac taaatcggaa ccctaaaggg agcccccgat ttagagcttg 300
acggggaaag ccggcgaacg tggcgagaaa ggaagggaag aaagcgaaag gagcgggcgc 360
tagggcgctg gcaagtgtag cggtcacgct gcgcgtaacc accacacccg ccgcgcttaa 420
tgcgccgcta cagggcgcgt ccattcgcca ttcaggctgc gcaactgttg ggaagggcga 480
tcggtgcggg cctcttcgct attacgccag ctggcgaaag ggggatgtgc tgcaaggcga 540
ttaagttggg taacgccagg gttttcccag tcacgacgtt gtaaaacgac ggccagtgaa 600
ttgtaatacg actcactata gggc 624

<210> 378
<211> 509
<212> DNA
<213> Homo sapiens

<400> 378
gttgttccag tttggaacaa gagtccacta ttaaagaacg tggactccaa cgtcaaaggg 60
cgaaaaaccg tctatcaggg cgatggccca ctacgtgaac catcacccta atcaagtttt 120
ttggggtcga ggtgccgtaa agcactaaat cggaacccta aagggagccc ccgatttaga 180
gcttgacggg gaaagccggc gaacgtggcg agaaaggaag ggaagaaagc gaaaggagcg 240
ggcgctaggg cgctggcaag tgtagcggtc acgctgcgcg taaccaccac acccgccgcg 300
cttaatgcgc cgctacaggg cgcgtccatt cgccattcag gctgcgcaac tgttgggaag 360
ggcgatcggt gcgggcctct tcgctattac gccagctggc gaaaggggga tgtgctgcaa 420
ggcgattaag ttgggtaacg ccagggtttt cccagtcacg acgttgtaaa acgacggcca 480

gtgaattgta atacgactca ctatagggc 509

<210> 379
<211> 654
<212> DNA
<213> Homo sapiens

<400> 379
aaatacgcat caggaaattg taagcgttaa tattttgtta aaattcgcgt taaatttttg 60
ttaaatcagc tcatttttta accaataggc cgaaatcggc aaaatccctt ataaatcaaa 120
agaatagacc gagatagggt tgagtgttgt tccagtttgg aacaagagtc cactattaaa 180

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<213> Homo sapiens

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<212> DNA
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<212> DNA
<213> Homo sapiens

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<210> 414
<211> 21
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<400> 414
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Asp Ala Asn Ser Tyr
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<210> 415
<211> 27
<212> PRT
<213> Homo sapiens

<400> 415
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Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp
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<210> 416
<211> 68
<212> PRT
<213> Homo sapiens

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Tyr Ser Leu Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met Ala
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Pro Ala Ser Ser
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<211> 27
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<213> Homo sapiens

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Pro Ser Ala Ser Pro Glu Glu Asp Glu Gly Ile
20 25